Efficacy and Safety of Oral Clindamycin in comparison with Doxycycline in Acne vulgaris

Dissertation submitted to

THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY

In partial fulfillment of the
regulations for the award of the degree of

M.D. (PHARMACOLOGY)

BRANCH-VI

GOVERNMENT STANLEY MEDICAL COLLEGE AND HOSPITAL

THE TAMIL NADU DR. MGR. MEDICAL UNIVERSITY
CHENNAI, INDIA

MARCH 2007

CERTIFICATE

This is to certify that this dissertation entitled "Efficacy and Safety of Oral Clindamycin in comparision with Doxycycline in Acne vulgaris" is a bonafide record of the research work done by DR. N. ARIVAZHAGAN for the award of MD degree in Pharmacology, under the supervision and guidance of DR. S. MADHAVAN, Professor and HOD of Pharmacology during the period between 2004-2007 in the Department of Pharmacology, Govt. Stanley Medical College, Chennai.

I also certify that this dissertation is the result of the independent work done by candidate.

Professor & Head of the Department
Department of Pharmacology
Govt. Stanley Medical College
Chennai – 600 001.

Dean
Govt. Stanley Medical College & Hospital
Chennai – 600 001.

DECLARATION

I solemnly declare that this dissertation, "Efficacy and Safety of Oral Clindamycin in comparision with Doxycycline in Acne vulgaris" was prepared by me in the Department of Pharmacology in collaboration with the Department of Dermatology, Government Stanley Medical College & Hospital, Chennai under the guidance and supervision of DR. S. MADHAVAN M.D, Professor & HOD, Department of Pharmacology, Government Stanley Medical College, Chennai between 2004 and 2007.

This dissertation is submitted to The Tamil Nadu DR. MGR Medical University, Chennai in partial fulfillment of the University requirements for the award of degree of M.D. in Pharmacology.

Place :

Date :

Dr.N. ARIVAZHAGAN

ACKNOWLEDGEMENT

I owe my deep felt gratitude to Dr. VASANTHI, M.D., former Dean, Government Stanley Medical College & Hospital, Chennai for helped me to get ethical committee approval and to conduct this study at Government Stanley Medical College Hospital.

I express my sincere gratitude to Dr.GUNASEKARAN, M.S. Dean, Government Stanley Medical College & Hospital, Chennai for permitting me to carry out this study at Government Stanley Medical College Hospital.

I express my sincere thanks to my guide, Dr. S. MADHAVAN, M.D., Professor & Head of the Department of Pharmacology, Govt. Stanley Medical College, Chennai for his inspiring guidance and the encouragement, throughout this study

I owe my sincere gratitude to Dr. A. M. JAYARAMAN M.D., D.D., Professor & Head of the Department of Dermatology, Stanley Medical College & Hospital, Chennai, as Co guide and permitting me to do this study in his department and for his valuable suggestions and support.

I thank Dr. R. NANDHINI, M.D., Former Professor of Pharmacology, Govt. Stanley Medical College for her encouragement in this study.

I express my sincere thanks to Dr. B. VASANTHI, M.D., Reader, Department of Pharmacology, Govt. Stanley Medical College, Chennai for her inspiration and motivation.

I thank Dr.R.SHANTHA RAMAN, MD, D.D., Asst Professor, Dept. of Dermatology, Govt. Stanley Medical College, Chennai for his suggestions in this study .

I extent my sincere thanks to Dr. PARIMALAM KUMAR, M.D, D.D., Asst Professor, Dept. of Dermatology, Govt. Stanley Medical College, Chennai for her encouragement in this study .

I extent my sincere thanks to Dr. K. VASANTHIRA, M.D., Former Assistant Professor of Pharmacology, Govt. Stanley Medical College, Chennai presently Reader of Pharmacology, Govt. Medical College, Chengalpat, for her encouragement in this study.

I thank Dr. R. ARUNKUMAR, M.D., Clinical Investigator, Malladi Drugs & Pharmaceuticals, Chennai, who had been a constant source of encouragement and moral support for the completion of this study.

I thank Dr. M. KULANDAIAMMAL, M.D., Asst Professor, Dept of Pharmacology, Govt. Stanley Medical College, Chennai for her encouragement in this study .

I thank Dr.J. JOTHILAKSHMI, M.D, Asst. Professor, Dept of Pharmacology, Stanley Medical College, Chennai for her encouragement in this study.

I thank Dr. R. Sivagami, Dr. K. Latha, Dr. Priestly vivek kumar,
Dr. Suguna Bai, Dr. B. Sharmila, Dr. Gomathi, Dr. Tiena sangeetha, presently the postgraduates, Department of Pharmacology, Govt. Stanley Medical College, Chennai, for their help during the study.

I wish to express my sincere thanks to M. Venkatesh, Statistitian, Govt. Stanley Medical College, Chennai.

I thank INDI PHARMA, Ponda, Goa, for providing the samples of Cap. Clindamycin, for this study.

Finally, I wish to express my sincere thanks to all the staff of Department of Pharmacology and Dermatology, Govt. Stanley Medical College & Hospital, Chennai for their co- operation in the completion of the study.

1. INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of pilosebaceous units. It is a common skin disorder affecting both boys and girls in the adolescent age group and also extends into the post adolescent age group.

Commonly it is due to formation of obstructing horny plugs in hair follicles, resulting in inflammation around the hair follicles, causing tissue destruction and scar formation.

This problem is present universally and affects people of all socio economic groups. With the improvement in the living status, awareness about acne is more among the affected age group causing psychological problems too.

From time immemorial, various remedies have been suggested and followed by Ayurvedic, Siddha, Unani practitioners and native healers present in various parts of the world.

The scientific evidence of improvement has not been documented yet. Modern medicine also prescribes various drugs, which have been found to be useful in controlling this disorder. All of them have been found to be useful to various extents.

Topical drug therapy has been the mainstay and some drugs, for example, tetracycline is given orally.

Since the condition results in scar formation and disfigurement in young boys and girls, it is associated with psychological problems causing great distress.

In this study an attempt has been made to evaluate the efficacy of a low dose oral Clindamycin in Acne vulgaris and the results of the study have been presented in ensuing chapters.

2. SCOPE OF THE STUDY

At present drugs are used topically in the form of gels, creams and alcohol-based lotions. The drugs used topically are antimicrobials and comedolytics.

Antimicrobial drugs are used orally. The antimicrobials administered orally are Tetracycline, Minocycline, Erythromycin and Doxycycline.

Since these oral antibiotics should be administered for more than two months, the incidences of adverse effects are also greater.

To mention, the risk of intracranial hypertension is more with the use of tetracycline orally for more than two months. [1]

Apart from this, other adverse reactions like super infection, Liver and kidney damage and other forms of skin reaction are also common.

Clindamycin is a lincosamide antibiotic which inhibits protein synthesis by binding to 50s ribosome.It is a semisynthetic antibiotic and derived from lincomycin by the addition of chloride.

The distinctive feature is its high activity against a variety of anaerobes. The usual oral dose is 150-300mgs 4 times a day for anaerobic infections. For Acne vulgaris topical clindamycin is found to be very effective.

The efficacy of oral clindamycin has not been evaluated, since high doses of 150-300 mgs given four times a day, causes pseudomembranous entero colitis due to clostridium difficle. This clindamycin is effective against propionibacterium acne that has been found to colonize the acne lesions.

Clindamycin has been used topically and is found to be effective. Therefore a study to evaluate a low dose of oral clindamycin in acne vulgaris was proposed and taken up. In this low dose, the beneficial effects without the risk of pseudomembranous colitis and other possible adverse effects have been evaluated.

3. AIM OF THE STUDY

Aim of the study is to evaluate the

- Efficay of oral clindamycin in comparison with doxycyclin in mild to modearte cases of acne vulgaris.
- Safety of oral clindamycin in comparison with doxycyclin in mild to modearte cases of acne vulgaris.

4. REVIEW OF LITERATURE

4.1. ACNE VULGARIS

4.2. BACTERIAL FLORA IN ACNE

4.2.1. Propioni bacterium Acne.

4.2.2. Staphylococcal epidermidis.

4.2.3. Pityriosporum ovale

4.3. BASIC PRINCIPLES OF TREATMENT

4.4. DRUG THERAPY OF ACNE VULGARIS

4.4.1. Topical agents,

4.4.1.1. Benzoyl Peroxide

4.4.1.2. Tretinoin.

4.4.1.3. Adapalene.

4.4.1.4. Topical antibiotics.

4.4.1.5. Azelaic acid.

4.4.2. Systemic agents

4.4.2.1. Antibiotics.

4.4.2.2. Oestrogen.

4.4.2.3. Isotretinoin.

4.4.2.4. Anti androgen.

4.1. ACNE VULGARIS

Acne vulgaris is a common skin disorder. About 70%_80% of people ,suffer from some sort of acne at one time or other. [2]

Acne vulgaris is prevalent in the age group 12-25 years.Though it is viewed as physiological reaction, the inflammatory changes which occur is disabling socially.[3]

Beyond the age of 23, Acne vulgaris seems to be more Prevalent among women.[4]

AETIOPATHOGENESIS

Acne vulgaris is a disease of pilosebaceous follicles. This is found maximally in face, chest and back. These are the primary sites of involvement. The basic cause is not known, and clinical Acne is due to interaction of various causes.

The earliest feature is increased sebum secretion; this is followed by formation of comedones or black heads. This comedones are follicular plugs made up of follicular debris and compacted sebum.[5]

The comedones have a pigmented tip caused by melanin deposition. Next there is colonization of pilosebaceous duct with propioni bacterium acne.

This is followed by inflammation in which reddened papules develop from the blocked follicles. They are tender and some times develope pus under the tips.

Propionibacterium acnes is non motile but easily colonizes the duct. To colonize, p.acnes organisms must clump; free fatty acids aid clumping, and so bacterial lipases may be nessary for clumping and duct colonization.[6]

Propionibacterium species are anaerobic coryne bacteria,reside in normal skin. Propionibacterium acnes,is aerotolerant and grows aerobically.It participates in the pathogenesis of acne by producing lipases that split free fatty acids off from skin lipids.These fatty acids can produce tissue inflammation and contribute to acne.[7]

I

Recent studies have shown that P.acnes binds to the receptors on monocytes and neutrophils then leads to the production of multiple Proinflammatory cytokines including interleukin12 (IL12), interleukin 8 (IL 8) and tumor necrosis factor (TNF)which in turn produces inflamation.[8]

The Four basic changes in acne vulgaris are

- Abnormal follicular keratinization and plugging of follicles along with increased sebum production.
- Comedogenesis.
- Colonization of duct with propionibacterium Acne.
- Inflammation. [9]

In severe cases central liquefaction occurs in the nodules, resulting in the formation of fluctuant cyst. The cysts have no real epithelial lining; so they are pseudocysts. When this nodules and cysts eventually subside they leave nodular scars,sometimes becoming hypertrophic or even keloidal.

Though the common areas are, lower jaw, chin, nose and forehead, in severe cases outer aspect of upper arms, buttocks and thighs are also involved.

Many factors are said to contribute like genetic factors, androgenic stimulation at the time of puberty and bacterial colonization as mentioned before.

Androgenic stimulation leads enlarged sebaceous glands with increased sebum production in both sexes.

It has also been found out that many patients with acne vulgaris do not have circulating androgens at pathological level. [10]

There may be an end organ sensitivity of the sebaceous glands to androgen stimulation or even that the circulating androgens are converted to a more potent androgen with in the sebaceous glands.[11]

Pathogenic bacteria are not found in Acne vulgaris. Only normal flora has a role to play.

The flora consists of Gram negative cocci like Staphylococcal Epidermidis, Gram -positive bacteria like Propionibacterium acne and also yeast like micro- organism known as pityriosporum ovale.

These known to colonize the sebaceous follicles and the Propioni bacterium is being most abundant.

4.2. BACTERIAL FLORA IN ACNE

Acne is not infectious; three major organisms isolated from the surface of the skin and pilosebaceous ducts of patients with Acne are;

4.2.1. Propioni bacterium Acne.

4.2.2. Staphylococcal epidermidis.

4.2.3. Pityriosporum ovale.[12]

Three major sub groups of Propioni bacterium acne are P. acnes, P. granulosum and P. avidum. Of this Propioni bacterium acnes is most important and to a lesser extent P.granulosum. These organisms live in association with

Staph epidermidis and M.furfur, the later organism have some control over the growth of P.acnes.[13]

It is possible that the number of microorganisms increase at each stage as the follicle progresses from normal to comedone and on to an inflamed lesion. The metabolic product includes propionic acid from which the genus name, Propioni bacterium derives .

4.2.1. PROPIONI BACTERIUM ACNES

It is an anaerobic corynebacterium and can also grow aerobically. It is a gram positive and nonmotile anaerobic bacteria.

It participates in the pathogenesis of Acne by producing lipases that split free fatty acids from skin lipid.

In adolescents there is increased seborrhoea and this is associated with significant increases in Grampositive nonmotile Propioni bacterium Acne.

The Propionibacterium acne is microaerophilic and lipophilic and therefore they live in depth of hair follicles in an oily milieu and they increase in number during puberty when the sebum secretion is also increased.[14]

The normal follicular flora may also be responsible for hydrolyzing the lipid esters of sebum, liberating potentially irritating fatty acids

The constituents of sebum and of skin surface lipid after the bacterial hydrolysis are as follow.

Sebum

Triglycerides

Cholesterol ester

Squalene

Wax esters

Skin surface lipid

Sebum lipids

Fatty acids

Monoglycerides

Diglycerides [15]

In gram stain, they are highly pleomorphic,showing curved,clubbed or pointed ends.

The dermal inflammation is not caused by bacteria but results from biologically active mediators they diffuse from follicle.

These mediators are produced by P.acnes. This bacteria brings about hydrolysis of lipid esters in sebum causing liberation of irritating fatty acids.

In vitro P.acnes produces many enzymes including three proteases, lipid phosphatases and hyaluronate lyase,all of which split protein and are implicated in the development of inflammation.[16]

4.2.2. Staphylococcus Epidermidis

The genus Staphylococcus has about 30 species; the clinically important ones are Staph. aureus, Staph. epidermidis, Staph. saprophyticus.

Staph.epidermidis are gram positive,nonpigmented coagulase negative cocci .

In infections due to implanted appliances and devices about 75% are caused by coagulase negative Staphylococcus epidermidis.[17]

Staph epidermidis is more resistant to antimicrobial drugs than is Staph aureus S. epidermidis infections are mostly hospital acquired.

The predisposing factors for Staph epidermidis infections are instrumentation procedures like catheterisation, heart valve implantations etc It has been found to cause infections in people who are immuno compromised and those who are on immuno suppressive therapy.[18]

Staphylococci are classified into slim produces and non slim produces.The ability to produce slim has been proposed as a marker for pathogenic strains of staphylococci.

Staph epidermidis produces a substance called slim.[19] This is a viscus extracellular glyco conjugate that allows Staph epidermidis to adhere to smooth surfaces such as prosthetic medical devices and the catheters.

Scanning electran microscopy has demonstrated that biofilms consisting of staphylococci encased in a slime matrix are formed in association with biomaterial associated infections.

Slime has been found to inhibit neutrophil chemotaxis, phagocytosis and the antimicrobial agents like vancomycin and Teicoplanin.

4.3. Basic Principles of treatment

Treatment may be aimed at

- Reducing the bacterial population of the hairfollicles to cutdown the hydrolysis of lipids – Antimicrobial agents.[20]
- Encouraging the shedding of the follicular horny plugs to free the obstruction – Comedolytic agents.
- Reducing the rate of sebum production, either directly by acting on the sebaceous Glands or indirectly by inhibiting the effects of androgens on the sebaceous glands –Anti androgens.
- Reducing the damaging effects of acne inflammation on the skin with anti inflammatory agents.

4.4. Drug Therapy for Acne vulgaris

4.4.1. Topical agents used are,

4.4.1.1. Benzoyl Peroxide

4.4.1.2. Tretinoin.

4.4.1.3. Adapalene.

4.4.1.4. Topical antibiotics.

4.4.1.5. Azelaic acid.

4.4.1.1. BENZOYL PEROXIDE

The most widely used topical drug is benzoyl peroxide, either as monotherapy or in combination. It reduces the number of non inflamed lesions.

It penetrates the stratum corneum or follicular openings and is converted metabolically to benzoic acid with in the epidermis and dermis.[21]

It is primarily antimicrobial and rapidly reduces both surface and ductal P.acnes. It acts by liberating oxygen and thus kills the organisms. It has high efficacy against P.acnes and has additional keratolytic and comdolytic properties.[22]

Organisms do not develop resistance to Benzoyl peroxide and it is mild irritant. It is used as 5% or 10% cream, Gel or lotion. It is effective in both inflammatory and non inflammatory Acne.

Benzoyl peroxide reduces the incidences of drug resistance when used in combination with antibiotics.

4.4.1.2. TRETINOIN

It is a comedolytic agent. It produces lysis of Keratinocytes and this Prevents formation of comedons. It has no antibacterial effect. It is used as Cream 0.025% to .05% and 0.1% , as a gel 0.01% and 0.025%. This can be alternated with Benzoyl peroxide. Retinoids are teratogenic and is contraindicated during pregnancy.[23]

Because it can be irritating on the skin, starting therapy with a lower concentration,less irritating cream and gradually working upto the more irritating gel and liquid forms makes patient compliance easier.

4.4.1.3. ADAPALENE

It is effective topical retinoid and has predominant anti comidonal activity. It binds to nuclear retinoic acid receptor and modulates keratinization and differentiation of follicular epithelial cells. Also it has anti-inflammatory action. It is as effective but less irritating than tretinoin and is available as 0.1% Gel.[24]

4.4.1.4. TOPICAL ANTIBIOTICS

- Tetracycline 2% - Less effective.
- Erythromycin 1-2% - quite effective for mild and moderate type of Acne.
- Clindamycin 2% - quite effective for mild and moderate type of Acne.

They are appropriate for cases with inflamed papules but less effective in non inflamed comedon formation in acnevulgaris. These antibiotics have low tendancy to sensitize and are not responsible for allergic contact dermatitis, though they may cause a minor degree of direct primary irritation.

Bacterial resistance to erythromycin frequently develops so it is used less often than other treatments.[25]

3.4.1.5. AZELAIC ACID

This is obtained from a natural product pityriasporum ovale. It is a straight chain saturated dicarboxilic acid effective in the treatment of acne vulgaris.[26]

It reduces cutaneous bacterial density, free fatty acid content of skin surface lipids and proliferation of keratinocytes.[27] It is used as 10% or 20% cream. Also it has anticomedogenic property.

4.4.2. SYSTEMIC THERAPY

Drugs used in Systemic Therapy and given orally are,

3.4.2.1. Antibiotics.

3.4.2.2. Oestrogen.

3.4.2.3. Isotretinoin.

3.4.2.4. Anti androgen.[27]

4.4.2.1. ANTIBIOTICS

Oral antibiotics are the most widely prescribed oral therapy world wide. Tetracycline is one of the drug which is commonly prescribed for acne vulgaris.

Oxytetracycline and Tetracyline are given dose of 250 mgs three times a day. The improvement usually begins only 4-8 wks after the commencement of treatment. Treatment may have to be maintained for several months.

Tetracyclines cause gastrointestinal discomfort, Diarrhoea and are teratogenic in pregnant women.[28]

4.4.2.1.1. DOXYCYCLINE

Doxycycline belongs to tetracycline group of antibiotics. It is an active congener of tetracycline. It is one of the most commonly prescribed antibiotics for the treatment of acne vulgaris, though oxytetracycline and tetracycline are also used for acne vulgaris among tetracyclines.[29]

MECHANISM OF ACTION

Doxycycline inhibit bacterial protein synthesis by binding to the 30s subunit of the ribosome and preventing access of amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site. Thus it inhibits bacterial protein synthesis. It is bacteriostatic in action.

Doxycycline enters the gram negative bacteria through passive diffusion through the hydrophilic channels formed by the porin proteins of the outer cell membrane. But it enters into the gram positive bacteria by an active transport by an energy dependent system that pumps it across the cytoplasmic membrane.[29]

PHARMACOKINETICS

Among all tetracyclines, doxycycline has got highest oral absorption (95%). However, taking it concomitantly with dairy foods decreases absorption because of the formation of non-absorbable chelates with calcium ions. Non absorbable chelates are also formed with other divalent and bivalent cations like Magnesium and Aluminium antacids.

Doxycycline is metabolized in liver to form soluble glucuronides. Most tetracyclines are excreted through kidney and are contraindicated in renal failure. But doxycycline is excreted through bile into the intestine. So it can be used in renal failure patients also.[29]

ADVERSE EFFECTS:

Adverse effects with doxycycline are few like nausea and vomiting usually not serious. Gastrointestinal discomfort and diarrhea occasionally occur. Photosensitivity is a problem only with old tetracyclines not with doxycycline.

PRECAUTIONS

It should be used with caution in patients with hepatic dysfunction and in conjuction with alcohol and other hepatotoxic drugs. It should not be given to pregnant women as it is teratogenic. It also causes bone and tooth abnormalities in children.

4.4.2.1.3. ERYTHROMYCIN

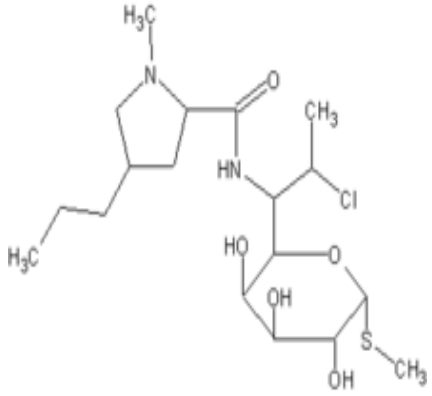
It is a macrolide antibiotic and a bacteriocidal drug. In acne it is effective as similar to tetracycline. Effective mostly against Gram positive and few Gram negative organisms. It causes inhibition of bacterial protein synthesis via binding to the 50s ribosomal RNA.. Erythromycin is preferable in the female who is or might, become pregnant or is breast feeding .[30]

Dose is 250 mg Q 6th hrly for first few weeks. Adverse effects like epigastric distress, hepatitis with cholestatic Jaundice. It can causes inhibition of CYP 3A4 when given along with Terfenadine, Astemizole and Cisapride.

4.4.2.1.5. CLINDAMYCIN

Clindamycin is a semisynthetic derivative of lincomycin. Chemically it is a derivative of trans-L-4-n propylhygrinic acid, attached to sulphur containing derivative of an octose. [31]

CHEMICAL STRUCTURE OF CLINDAMYCIN



Clindamycin

Methyl-6-amino-7-chloro-6,7,8-trideoxy-N-

[(2S,4R)-1-methyl-4-propylprolyl]-

1-thio-β-L-threo-D-galacto-octopyranoside

IUPAC name

MECHANISM OF ACTION

It binds to 50s ribosomal subunit of bacteria and suppresses protein synthesis. Mechanism of action resemble erythromycin and Chloramphenicol, though they are not structurally related. They act at site with in close proximity,and binding by one of these antibiotics to the ribosome may inhibit the interaction of the others.

It inhibits more Gram positive cocci including penicillinase producing staphyllococcus but not methicillin producing Staphylococcus and other Gram positive organisms like Clostridium Diphtheria, Nocardia, Actinomycosis and Toxoplasma.

The distringtive feature is its high activity against anaerobes especially bacteroides fragilis. It is not active against anaerobic Gram negative bacilli.[31]

PHARMACOKINETICS

It is given orally, well absorbed and food does not reduce the absorption.The plasma half life(t½) of 150 mg given orally is 2.9 hrs and usually given at 6th hourly intervals.

It is widely distributed in body fluids and tissues including bone but CSF concentration is poor.[31]

Clindamycin accumulates in polymorphonuclear leucocytes, alveolar macrophages and abscesses. It is demethylated to inactive metabolites and excreted in urine and bile.

AVAILABILITY

It is available as 150 mg and 300mg capsules. Injections of 300mg/2mland 600 mg/4ml is also available. The preparation which is given parenterally is phosphate ester which is rapidly hydrolysed to active parent compound in the body.

For Paediatric use, it is available as Clindamyein palmitate and it is an inactive prodrug.[31]

DOSAGE

Oral dosage is 150 – 300 mg every 6th hourly .For children clindamycin palmitate is 8 – 12 mg/kg/day in divided doses.

For serious infections caused by susceptible organisms the drug is given intravenously and intramuscularly in the dose of 600 – 1200 mg /day in two to four divided doses.

INDICATIONS

- Infection caused by anaerobic Gram positive cocci.[32]

- For Gram negative organisms. For this it is more effective when combine with aminoglycoside.
- Clindamycin given intravenously along with oral dose of pyremethamine has been found to be effective in encephalitis caused by Toxoplasma gondi in AIDS.[32]
- Clindamycin combination with oral primaquine has been found to be useful for pneumocystitis carini infection in AIDS Patients [32]
- Clindamycin topical in the form of solution, gel or lotion are used for acne vulgaris caused by propionibacterium acne.
- Clindamyin Vaginal Cream for bacterial Vaginosis.

ADVERSE EFFECTS

- It causes diarrhoea, pseudomembranous enterocolitis may occur due to clostridium difficle infection.
- Patient present with abdominal pain, diarrhoea, fever and passage of mucous and blood in the stools, can be lethal.
- Skin rashes can occur.
- Rarely erythema multiforme.
- Reversible elevation of Aspartate amino transferase and Alamine aminotransferase.
- Granulocytopenia, thrombocytopenia.
- Intravenous administration causes thrombophlebitis.

DRUG INTERACTIONS

- Clinidamycin can inhibit neuromuscular transmission and potentiates the effect of Neuro musclear blockers [32]
- Drugs like opioids which reduce peristalsis, they prolong and worsen pseudomembrano entero colitis.

4.4.2.2. OESTROGENS

It can be used in girls above 16 years. Ethinyloestrodiol is given at the dose of 35-50 µg/day from 5^{th} to 25^{th} day of the menstrual cycle.

It acts by suppressing Androgenic stimulation of sebaceous follicle.[33]

Their use is best restricted to women over 16 yrs old with recalcitrant severe pustolocystic acne. Side effects include nausea, weight gain, hypertension and thromboembolism.

4.4.2.3. ISOTRETINOIN (13-CIS RETINOIC ACID)

It is orally administered retinoid. It reduces the production of sebum by shrinking the sebaceous glands. It has effect on the keratinization of the mouth of the hair follicle and an anti inflammatory action as well. The clearance of skin bacteria also occurs secondary to reduction in sebum production.

The usual dose is 0.5 to 1 mg/ kg body weight per day for 16 weeks.

The adverse effects are dryness of skin, eyes, nose and mouth, cracking of lips, epistaxis, pruritus etc. Isotretinoin is also teratogenic drug.[34]

It produces hepatotoxicity, bone toxicity, depression, psychosis and rarely suicidal thoughts or attempts.

4.4.2.4. ANTI ANDROGEN

These drugs Inhibit androgenic activity and reduces sebum secretion. Reducing the rate of sebum production will lessen the tendency to form comedons and reduce the number of inflammatory lesions.

Cyproterone acetate, an antiandrogen is used at the dose of 100mg on days 5 --15 of menstrual cycle.

Anti androgens are available as a mixture of Cyproterone acetate 2mg an antiandrogen with oestrogen ethinyl oestradiol 35µgm.[35]

It competitively inhibits the testosterone receptors or androgenic receptors in target peripheral organs. It is not frequently used in Acnevulgaris therapy. It is not suitable for men because of its feminizing properties.

5. MATERIALS AND METHODS

STUDY CENTER

Out Patient Section,

Department of Dermatology,

Govt. Stanley Medical College & Hospital, Chennai.

STUDY PERIOD

September 2005 to May 2006.

STUDY DURATION FOR EACH PATIENT

Total six weeks.

Drug administration - four weeks.

Follow up - two weeks.

STUDY DESIGN

Prospective, Randomized Controlled, Single blind study.

DRUGS USED

Capsule Clindamycin 50 mg.

Capsule Doxycycline 100 mg.

Benzoyl Peroxide 5 % topical cream.

SOURCE OF DRUGS

Capsule Clindamycin, supplied by Indi pharma, Ponda, Goa.

Capsule Doxycycline routinely available in the dispencery of Govt. Stanley Medical College Hospital.

STUDY PLAN

When the study was planned, it was first proposed to evaluate the safety and efficacy of oral Clindamycine with oral Doxycycline.

On review the literature, Acne Vulgaris is found to have various steps in the pathogenesis and the drugs currently used act at different steps. Hence it was decided to include two more groups, in which the patients receiving oral Clindamycine along with topical Benzoyl peroxide are compared with another group receiving oral Doxycycline along with topical Benzoyl Peroxide .

This study in addition to giving information about the safety and efficacy of oral Clindamycine used in low doses,and also give valuable information about the efficacy rate,in combination with topical benzoyl peroxide.

STUDY DESIGN

The Study was started after getting the approval from institutional ethical committee.

Patients were included only after obtaining the informed written consent. In patients who were less than 18 years old, the consent was obtained from parents also. A copy of the consent form is attached (Appendix I).

INCLUSION CRITERIA

Patients who are

- Having mild to moderate acne vulgaris with the lesions only on cheek, forehead, chin, nose and neck (above clavicle).
- Both males and females of 15 years to 25 years.
- Willing to give written informed consent.
- Suffering from acne vulgaris for three or more months.
- Not under drug therapy for acne vulgaris.
- Not suffering from any systemic illness.

EXCLUSION CRITERIA

Patients who are

- Having severe acne vulgaris
- Below 15 years and above 25 years.
- Suffering from systemic illness like cardiac valvular lesions, Diabetes mellitus, Hypertension and congenital anomalies.
- Not willing to give informed written consent.
- With the history of hypersensitivity to antimicrobials.

METHODOLOGY

The study is conducted as four different trials. In each trial totally 60 patients are selected and are randomly divided in to 2 groups, group A and B.

TRIAL I

In trial I, 60 patients suffering from mild acne vulgaris are included and are randomly allotted in to group A and B, with 30 patients in each group.

Group A patients are treated with oral Doxycycline 100 mg, once daily, in the morning, after food, for four weeks. Group B patients are treated with oral Clindamycin 50 mg once daily in the morning, after food, for four weeks.

The patients are assessed before starting drug therapy and after drug administration, at the end of 1st week, 2nd week, 3rd week and at the end of 4th week.

The patients are also assessed during the follow up visits at the end of 5th and 6th weeks.

TRIAL II

In this trial also, 60 patients suffering from mild acne vulgaris are included and are randomly allotted in to group A and B, with 30 patients in each group.

But here, Group A patients are treated with 5% topical Benzoyl peroxide applied during bed time every day for 4 weeks, in addition to oral Doxycycline 100 mg given once daily, in the morning, after food, every day for four weeks.

Group B patients are treated with 5% topical Benzoyl peroxide applied during bed time every day for 4 weeks, in addition to oral clindamycin 50 mg given once daily, in the morning, after food, every day for four weeks.

The patients in both the groups are assessed before starting therapy and at the end of every week as done in Trial I.

TRIAL III

In Trial III, 60 patients suffering from moderate acne vulgaris are included and are randomly allotted in to group A and B, with 30 patients in each group.

Group A patients are treated with oral Doxycycline 100 mg, once daily, in the morning, after food, every day for four weeks. Group B patients are treated with oral clindamycin 50 mg once daily in the morning, after food, every day for four weeks.

The patients are assessed before and after drug therapy in the similar way followed in trial I and II.

TRIAL IV

In trial IV, like trial III, 60 patients suffering from moderate acne vulgaris are included and are randomly allotted in to group A and B, with 30 patients in each group.

Here Group A patients are treated with 5% topical Benzoyl peroxide applied during bed time every day for 4 weeks, in addition to oral Doxycycline 100 mg given once daily, in the morning, after food, every day for four weeks.

Group B patients are treated with 5% topical Benzoyl peroxide applied during bed time every day for 4 weeks, in addition to oral clindamycin 50 mg given once daily, in the morning, after food, every day for four weeks.

ASSESMENT CRITERIA

Acne vulgaris is classified into Grade I, II, II and IV depending upon the presence of comedons, papules and pustules.

Grade I (mild) – Comedons & occasional papules.

Grade II (moderate) – Comedons, papules & few pustules.

Grade III (severe) – Pustules, nodules & abscesses.

Grade IV (cystic) – Very severe form consists of cysts, Abscesses & Scarring.

In this study, only grade I (mild) & grade II (moderate) patients are included and grade III and grade IV patients are not included.

The effect of drugs in reducing the number of comedons, papules and pustules in all the four trial groups are recorded before starting treatment and at the end of every week for six weeks.

The model of proforma used for the study is given in the appendix II.

The results are assessed both clinically and statistically in all the four trials.

6. RESULTS

The results of the study conducted to evaluate the safety and efficacy of oral dose of 50 mg of Clindamycin administered daily for a period of four weeks in comparision with oral Doxycycline are presented and analysed.

The purpose of using topical Benzoyl peroxide 5% cream is to see if the benefit arising out of combination therapy is better than single drug therapy or not.

RESULTS OF TRIAL I

THE EFFECT OF DRUGS ON COMEDONS IN MILD CASES OF ACNE

When Doxycycline is administered orally for four weeks in 30 patients, on zero visit that is before drug administration, the arithmetical mean of number of comedons was 4.40 and this has come down to 3.06 at the end of six weeks.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	4	4	4	3	3	4
2	4	3	3	4	3	3	3
3	5	3	3	4	3	4	4
4	4	4	4	3	3	2	3
5	5	3	3	4	4	4	2
6	3	3	3	4	3	3	3
7	5	5	4	2	3	4	3
8	5	5	3	4	4	3	2
9	4	4	3	4	2	2	3
10	5	4	4	4	4	3	3
11	4	3	4	2	3	3	4
12	4	3	4	3	4	2	3
13	4	5	5	3	3	3	4
14	3	5	4	5	2	3	3
15	5	4	3	3	3	4	2
16	5	4	4	3	3	3	3
17	5	5	4	4	2	4	3
18	5	5	5	4	3	3	3
19	4	4	4	3	3	2	4
20	5	3	4	4	4	3	3
21	4	4	4	3	4	3	4
22	3	5	5	3	3	2	3
23	5	4	3	4	4	3	2
24	5	3	5	3	3	3	3
25	4	5	5	3	4	4	3
26	4	4	3	4	4	4	2
27	5	3	3	3	3	3	3
28	5	5	4	3	2	4	3
29	4	4	4	3	3	3	4
30	5	4	3	2	3	4	3
Mean	4.4	4	3.8	3.4	3.16	3.13	3.06

Table 1 No. of comedons in each patient in group A of trial I

In Clindamycin administered group, the arithmetical mean of number of comedons, 4.33 on '0' visit that is before drug administration has come down to 2.83 after 6 weeks of drug administration.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	3	4	4	3	3	3
2	5	3	5	4	4	2	4
3	4	5	3	3	3	3	3
4	4	1	4	3	2	3	2
5	4	1	4	1	2	2	3
6	3	4	3	4	2	3	3
7	5	3	4	4	3	4	2
8	5	3	4	3	3	3	4
9	5	5	4	1	2	2	2
10	5	1	1	3	4	3	4
11	4	2	4	5	3	4	3
12	5	4	4	3	4	3	3
13	4	5	1	1	3	3	3
14	3	5	4	4	2	4	4
15	5	4	3	3	4	3	3
16	5	3	2	2	4	2	2
17	4	2	1	2	3	3	2
18	4	5	3	3	4	4	4
19	5	4	4	3	2	1	3
20	5	3	3	4	3	3	2
21	4	1	3	2	4	3	3
22	5	4	4	1	3	4	3
23	4	5	3	2	2	2	3
24	3	4	1	3	4	2	2
25	5	4	2	4	3	3	3
26	5	2	3	3	1	4	2
27	4	5	4	3	2	3	1
28	4	4	2	3	2	3	4
29	5	3	1	4	3	4	3
30	3	5	4	3	2	3	2
Mean	4.33	3.43	3.06	2.93	2.86	2.96	2.83

Table 2 No. of comedons in each patient in group B of trial I

THE EFFECT OF DRUGS ON PAPULES IN MILD CASES OF ACNE

In **Doxycycline** administered group the arithmetical mean of number of papules in 30 patients on '0'visit that is before drug administration was 3.30 and it has come down to 2.2 at the end of sixth week .

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	2	2	3	2	2	1
2	4	3	1	2	3	3	2
3	3	3	2	3	1	2	2
4	4	2	1	3	3	1	2
5	3	2	2	2	1	1	2
6	4	3	3	3	2	3	3
7	2	3	2	2	3	2	3
8	3	2	3	1	1	3	2
9	4	4	3	2	2	2	3
10	2	2	3	1	2	3	1
11	3	3	2	2	3	3	2
12	4	3	4	3	1	2	3
13	3	4	2	3	3	2	2
14	3	2	4	1	2	3	2
15	4	3	3	2	1	2	2
16	4	2	2	3	3	3	3
17	3	3	4	2	2	2	1
18	4	3	3	3	2	2	2
19	2	2	1	3	3	2	2
20	3	3	2	3	2	2	3
21	4	4	2	3	2	3	2
22	3	3	2	2	3	2	2
23	4	2	3	2	4	1	2
24	4	3	2	3	3	2	3
25	3	3	3	3	2	2	3
26	4	2	2	2	2	2	2
27	2	3	3	3	3	3	3
28	3	2	2	1	2	2	3
29	4	4	4	2	2	3	1
30	2	2	3	2	2	0	2
Mean	3.3	2.73	2.5	2.33	2.23	2.16	2.2

Table 3 No. of papules in each patient in group A of trial I

In the case of Clindamycin administered group the arithmetical mean of number of the papules in 30 patients on '0' visit that is before drug administration was 3.36 and it has very significantly come down to 1.9 at the end of sixth visit.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	2	3	1	2	2	1	1
2	3	2	2	3	3	3	2
3	4	4	2	1	1	2	2
4	2	2	3	2	2	1	3
5	3	3	2	3	2	3	2
6	4	3	2	1	3	2	0
7	3	1	2	2	2	2	2
8	3	2	2	2	3	1	1
9	4	3	2	3	1	3	1
10	4	2	3	1	0	0	2
11	3	1	2	2	1	2	2
12	4	3	2	2	1	1	3
13	4	2	3	1	2	1	2
14	3	3	1	2	1	2	2
15	4	1	2	2	2	1	2
16	4	3	2	2	2	2	2
17	3	2	2	1	3	2	3
18	4	3	2	2	1	3	3
19	4	3	3	2	3	2	1
20	3	2	2	3	2	3	0
21	4	2	3	1	1	3	2
22	2	2	2	2	3	1	2
23	3	3	2	3	2	3	3
24	4	3	2	3	2	2	2
25	3	2	3	2	1	2	1
26	3	2	2	4	2	3	2
27	4	3	2	2	1	3	2
28	3	2	2	1	3	1	2
29	3	3	3	2	1	2	3
30	4	2	0	3	2	1	2
Mean	3.36	2.4	2.1	2.06	1.83	1.93	1.9

Table 4 No. of papules in each patient in group B of trial I

RESULTS OF TRIAL II

THE EFFECT OF DRUGS ON COMEDONS IN MILD CASES OF ACNE

The arithmetical mean of the number of comedons in one group of thirty patients who receive oral Doxycycline along with topical Benzoyl peroxide was 4.33 on '0'visit that is before starting therapy. The arithmetic mean at the end of sixth visit has come down to 2.0.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	4	3	3	3	3	3
2	4	4	3	1	2	2	3
3	3	3	4	3	3	2	0
4	5	3	4	1	3	0	3
5	5	5	4	2	4	3	1
6	5	5	5	3	3	2	3
7	5	4	4	1	4	3	2
8	4	4	3	4	1	0	3
9	5	5	2	4	2	3	1
10	4	5	4	2	3	3	3
11	3	4	3	1	0	4	2
12	5	3	4	1	1	3	2
13	5	4	3	2	3	0	3
14	4	5	3	0	4	1	2
15	3	3	1	1	3	3	2
16	5	3	3	3	1	3	0
17	5	1	3	3	1	2	2
18	4	4	3	2	2	3	2
19	4	3	2	3	3	1	1
20	5	3	3	2	3	3	4
21	5	5	3	3	1	2	1
22	4	1	4	1	2	3	3
23	5	4	1	2	1	2	2
24	4	4	3	1	0	1	2
25	3	2	5	3	2	3	1
26	5	4	4	2	3	2	1
27	5	4	2	3	0	3	2
28	4	1	1	3	2	1	3
29	3	3	1	1	1	0	2
30	5	4	2	0	2	2	1
Mean	4.33	3.56	3	2.03	2.1	2.1	2

Table 5 No. of comedons in each patient in group A of trial II

In other group which was treated with oral Clindamycin along with topical Benzoyl peroxide the arithmetical mean come down to 1.1 at the end of sixth visit from 4.6 the mean before treatment.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	3	3	4	2	1	0	2
2	5	4	3	3	3	0	3
3	5	4	2	3	2	1	0
4	4	3	3	1	1	0	1
5	4	4	3	3	1	1	0
6	5	3	4	0	1	3	1
7	5	3	3	3	3	2	0
8	4	4	4	2	0	1	0
9	5	3	3	1	0	0	0
10	4	4	2	2	0	1	1
11	5	4	3	0	1	1	1
12	5	4	2	1	1	2	1
13	5	5	2	0	1	0	1
14	5	4	3	0	0	1	1
15	4	3	3	3	1	1	1
16	5	4	4	2	1	2	2
17	5	4	4	1	1	1	3
18	5	3	2	1	1	1	1
19	5	4	4	1	2	1	3
20	4	5	3	3	1	2	1
21	5	3	4	2	2	2	1
22	5	4	3	0	1	0	2
23	3	3	5	2	0	2	0
24	5	3	3	0	3	1	0
25	5	3	3	2	0	0	3
26	4	4	4	1	1	1	0
27	5	3	3	2	2	2	0
28	5	2	2	0	1	0	2
29	5	4	2	2	0	1	2
30	4	2	3	1	0	1	0
Mean	4.6	3.53	3.1	1.46	1.06	1.03	1.1

Table 6 No. of comedons in each patient in group B of trial II

THE EFFECT OF DRUGS ON PAPULES IN MILD CASES

The arithmetical mean of the number of papules in one group of thirty patients who receive oral Doxycycline along with topical Benzoylperoxide was 3.56 on '0'visit that is before starting therapy. The arithmetic mean at the end of sixth visit hss come down to 1.6.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	2	3	2	2	1	2
2	4	3	1	3	2	1	2
3	3	3	2	1	0	2	3
4	4	1	2	2	3	1	2
5	4	2	3	2	2	2	3
6	3	3	1	1	2	2	3
7	4	2	2	2	2	3	2
8	4	1	2	2	1	2	2
9	3	3	2	2	2	3	1
10	4	2	2	1	0	3	3
11	4	3	2	2	2	2	0
12	3	1	2	2	1	2	2
13	4	3	0	3	1	1	1
14	3	2	1	2	2	3	1
15	4	3	3	2	1	0	1
16	3	2	2	2	2	2	0
17	3	1	1	2	2	2	2
18	4	3	2	0	3	1	2
19	4	2	2	3	2	2	1
20	3	3	3	2	3	0	2
21	4	1	1	2	3	0	1
22	4	3	3	2	2	1	2
23	3	2	2	1	2	1	1
24	4	3	2	2	1	2	1
25	4	3	2	2	0	0	2
26	3	3	2	0	0	2	1
27	3	3	3	1	2	2	1
28	4	2	1	2	1	1	1
29	3	2	2	2	1	1	2
30	3	2	2	0	1	0	1
Mean	3.56	2.3	1.93	1.73	1.6	1.5	1.6

Table 7 No. of papules in each patient in group A of trial II

In case of papules, the group of thirty patients treated with oral Clindamycin along with topical Benzoylperoxide the corresponding values are 3.56 before therapy and 0.86 at the end of sixth week. This is also clinically significant.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	2	1	1	1	1	0
2	4	3	3	2	0	1	1
3	3	1	0	0	2	2	1
4	4	2	2	2	0	2	0
5	4	2	2	0	2	1	0
6	3	1	1	2	1	1	2
7	4	2	2	0	1	0	1
8	4	2	0	2	0	2	2
9	3	3	0	1	2	1	1
10	3	4	1	2	0	1	0
11	4	3	1	0	2	2	2
12	3	2	2	1	2	0	0
13	3	2	0	2	0	0	1
14	4	3	2	1	0	0	1
15	3	2	2	1	0	0	2
16	3	2	1	0	2	1	1
17	4	2	3	2	0	1	2
18	4	2	2	3	1	1	2
19	3	3	3	3	1	0	0
20	4	2	3	2	0	0	1
21	3	2	2	2	0	1	0
22	4	2	2	1	0	0	1
23	3	0	1	1	1	0	1
24	3	2	3	0	2	1	1
25	4	3	0	2	0	1	0
26	4	2	2	2	0	0	1
27	3	1	2	1	0	0	1
28	4	2	1	2	0	2	0
29	4	2	2	0	0	0	0
30	4	1	2	1	1	0	1
Mean	3.56	2.06	1.6	1.3	0.7	0.73	0.86

Table 8 No. of papules in each patient in group B of trial II

RESULTS OF TRIAL III

THE EFFECT OF DRUGS ON COMEDONS IN MODERATE CASES OF ACNE

Here in the group of 30 patients who received oral Doxycycline, the arithmetical mean of number of comedons before therapy 4.73 and at the end of sixth week it is 3.06.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	5	4	3	2	3	3
2	5	3	4	3	3	4	3
3	5	5	5	2	3	3	3
4	4	5	3	3	5	2	4
5	5	4	4	3	3	3	3
6	4	4	3	4	3	3	4
7	4	4	4	3	4	2	4
8	4	4	3	4	4	3	2
9	4	5	3	4	3	3	3
10	5	5	4	4	4	4	3
11	5	4	4	3	3	3	2
12	5	4	3	4	3	4	3
13	5	4	5	4	4	3	3
14	4	5	4	5	3	4	2
15	5	4	3	3	3	4	3
16	5	5	4	4	3	2	3
17	5	5	4	4	4	4	4
18	5	4	3	2	3	3	3
19	5	3	4	3	3	4	3
20	4	5	4	3	4	3	4
21	5	4	3	4	2	2	3
22	5	4	4	3	4	3	4
23	5	4	5	3	3	3	3
24	5	3	4	3	2	2	4
25	5	3	3	4	3	3	3
26	5	5	5	3	2	4	3
27	5	4	4	3	3	4	2
28	5	3	3	2	3	3	3
29	5	4	5	3	2	2	3
30	5	4	4	4	3	3	2
Mean	4.73	4.16	3.83	3.33	3.13	3.1	3.06

Table 9 No. of comedons in each patient in group A of trial III

In another group of 30 patients who received only oral clindamycin the arithmetical mean is 4.66, before therapy has come down to 2.66 at the end sixth week.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	4	3	2	2	3	2
2	4	1	4	3	3	2	3
3	5	4	4	3	1	3	3
4	5	2	3	4	4	2	2
5	5	5	5	2	4	3	3
6	5	4	4	3	3	4	3
7	4	3	3	3	4	4	1
8	5	5	4	4	3	2	3
9	5	5	4	3	3	1	3
10	5	2	3	3	1	3	4
11	5	4	4	2	3	4	3
12	5	3	4	3	3	3	1
13	4	3	3	3	3	2	3
14	5	4	4	4	1	3	4
15	5	5	5	3	3	1	3
16	4	4	4	4	3	2	1
17	5	4	3	2	4	3	4
18	4	5	5	4	1	3	2
19	4	5	3	2	4	4	3
20	4	4	4	4	3	3	3
21	4	5	3	4	4	1	2
22	5	4	4	5	3	3	3
23	5	5	3	3	3	4	2
24	5	4	3	4	4	4	2
25	5	5	4	4	3	2	3
26	4	5	4	2	3	1	3
27	5	4	3	3	3	3	2
28	5	4	5	3	4	4	3
29	5	5	4	4	3	3	3
30	5	4	3	2	3	2	3
Mean	4.66	4.03	3.73	3.16	2.96	2.73	2.66

Table 10 No. of comedons in each patient in group B of trial III

THE EFFECT OF DRUGS ON PAPULES IN MODERATE CASES OF ACNE

In case of Doxycycline treated group the arithmetical mean of papules on '0' visit that is before drug therapy was 3.56 and at the end sixth week it was 2.36.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	3	3	3	2	3	2
2	3	3	3	2	3	2	3
3	4	2	2	3	1	3	2
4	4	4	4	2	2	2	2
5	3	2	2	1	2	3	2
6	4	3	4	2	3	3	3
7	3	3	3	1	1	4	1
8	4	4	2	2	3	2	2
9	4	2	4	3	2	3	2
10	4	3	3	3	1	2	3
11	3	4	1	1	3	3	2
12	4	3	2	2	2	2	2
13	2	3	2	3	2	2	2
14	3	2	2	2	3	2	3
15	4	3	3	3	2	2	3
16	3	4	2	3	2	2	2
17	4	3	3	3	3	1	3
18	4	2	2	4	3	4	3
19	3	3	1	3	3	3	3
20	4	3	2	2	2	2	3
21	4	4	3	3	2	3	2
22	4	2	2	1	3	2	3
23	4	3	3	2	2	3	1
24	4	3	3	2	1	3	2
25	3	4	3	4	3	2	3
26	4	4	2	2	2	2	2
27	3	4	4	1	2	3	4
28	4	4	2	2	3	1	2
29	3	2	4	4	4	2	2
30	4	2	3	2	3	2	2
Mean	3.6	3.03	2.63	2.36	2.33	2.43	2.36

Table 11 No. of papules in each patient in group A of trial III

In Cindamycin treated group the corresponding values are 3.53 and 1.96 before therapy and at the end of sixth week respectively.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	4	3	1	2	1	1
2	3	2	3	2	1	1	2
3	3	3	3	1	1	1	1
4	4	3	3	2	3	3	1
5	4	4	2	1	2	2	2
6	3	3	3	2	2	3	2
7	4	3	1	3	3	2	2
8	2	2	2	3	2	3	3
9	3	3	2	2	1	3	3
10	4	3	4	2	3	2	2
11	3	2	2	3	2	2	3
12	4	3	2	2	2	1	3
13	4	4	2	3	3	1	1
14	3	3	1	3	1	2	3
15	4	2	2	1	3	2	1
16	4	3	2	2	3	3	1
17	3	2	1	3	1	2	1
18	4	3	2	2	2	3	2
19	4	3	3	1	2	2	2
20	2	2	2	1	1	2	3
21	3	3	3	3	3	2	1
22	4	4	3	3	2	2	2
23	3	3	3	1	2	2	2
24	4	3	3	2	1	1	3
25	4	3	3	1	2	1	2
26	3	3	2	2	2	1	2
27	4	2	3	2	1	2	3
28	4	4	3	3	0	2	2
29	4	2	3	2	2	3	1
30	4	2	2	3	1	1	2
Mean	3.53	2.86	2.43	2.06	1.86	1.93	1.96

Table 12 No. of papules in each patient in group B of trial III

THE EFFECT OF DRUGS ON PUSTULES IN MODERATE CASES OF ACNE

In case of Doxycycline treated group the arithmetical mean of number of pustules before treatment is 3.26 and 2.03 at the end of sixth week.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	2	2	2	2	2	2	3
2	3	4	3	1	2	2	4
3	4	3	2	2	3	0	0
4	3	3	2	3	1	2	2
5	4	3	2	3	2	2	1
6	2	4	3	1	2	2	1
7	4	2	3	2	3	0	2
8	3	3	2	2	2	3	3
9	4	3	3	2	2	2	2
10	2	2	3	3	2	3	2
11	3	1	3	3	3	2	2
12	4	3	3	3	3	3	3
13	3	3	2	1	2	0	2
14	4	1	3	3	3	2	3
15	4	4	1	2	2	1	2
16	3	2	2	1	3	2	3
17	4	3	3	2	4	3	0
18	4	3	3	1	3	4	2
19	4	2	3	2	2	0	1
20	3	2	2	2	1	2	2
21	4	4	2	1	1	1	3
22	3	3	3	4	2	1	4
23	4	3	2	3	1	2	4
24	3	2	1	2	2	3	3
25	2	2	3	3	1	2	2
26	3	3	2	2	2	2	1
27	4	2	2	1	1	2	1
28	2	1	3	2	0	1	2
29	2	3	3	1	2	1	1
30	4	4	3	2	1	1	0
Mean	3.26	2.66	2.46	2.06	2	1.76	2.03

Table 13 No. of pustules in each patient in group A of trial III

In Clindamycin treated group the corresponding values are 3.36 and 1.36 before therapy and at the end of sixth week respectively

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	3	2	1	2	1	3	0
2	4	3	2	1	2	2	2
3	3	3	3	0	0	0	3
4	4	3	1	1	2	2	2
5	4	2	1	2	1	1	3
6	3	1	3	2	1	1	0
7	4	3	3	2	2	2	3
8	4	3	1	3	1	0	0
9	4	2	2	3	2	2	2
10	3	2	2	3	1	2	1
11	4	3	1	1	2	0	0
12	3	2	2	3	1	1	3
13	4	2	3	2	0	1	1
14	3	3	0	1	2	0	1
15	4	3	2	2	1	1	3
16	2	2	3	1	3	1	2
17	4	2	3	2	1	2	1
18	3	3	0	2	2	3	1
19	4	3	3	1	2	2	2
20	2	3	2	2	3	1	1
21	3	2	3	1	2	0	0
22	4	2	2	2	2	1	0
23	3	3	2	3	2	0	1
24	2	3	3	3	1	2	2
25	2	4	3	1	2	3	1
26	4	2	3	2	2	4	1
27	4	2	1	2	3	0	2
28	3	3	2	1	1	2	1
29	4	2	3	1	0	1	0
30	3	3	2	1	0	0	2
Mean	3.36	2.53	2.06	1.76	1.5	1.33	1.36

Table 14 No. of pustules in each patient in group B of trial III

RESULTS OF TRIAL IV

THE EFFECT OF DRUGS ON COMEDONS IN MODERATE CASES OF ACNE

The group treated with oral **Doxycycline** along with topical **Benzoyl peroxide** the arithmetical mean of number of comedons was 4.66 on "0" visit that is before drug therapy and 1.86 at the end of sixth week.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	2	5	3	1	2	1
2	5	5	4	0	1	3	4
3	5	4	3	2	3	4	3
4	5	3	1	0	3	0	1
5	5	5	4	3	2	2	3
6	5	4	3	2	3	1	4
7	4	1	4	4	4	3	0
8	5	4	2	5	3	1	4
9	5	3	3	3	2	3	3
10	4	3	4	0	3	1	2
11	5	4	1	3	2	2	1
12	4	4	4	3	0	1	3
13	4	4	3	2	3	1	1
14	4	1	2	3	2	1	2
15	4	4	3	3	0	0	1
16	5	4	1	2	2	1	2
17	5	4	3	3	3	3	0
18	5	3	2	1	1	2	3
19	5	3	1	0	2	1	0
20	4	4	3	3	1	1	1
21	5	4	1	0	3	4	3
22	5	4	1	3	1	3	0
23	5	4	3	3	0	0	3
24	5	5	2	4	1	3	1
25	5	5	0	3	3	2	3
26	4	4	3	0	1	0	1
27	5	4	4	3	3	1	3
28	5	3	2	2	2	3	2
29	4	5	4	2	3	0	1
30	5	3	3	1	2	1	0
Mean	4.66	3.66	2.63	2.2	2	1.66	1.86

Table 15 No. of comedons in each patient in group A of trial IV

In case of oral **Clindamycin** along with topical **Benzoyl peroxide** the values recorded are 4.7 before therapy and 0.96 at the end of sixth week.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	5	3	0	3	1	1	2
2	5	2	2	2	1	0	0
3	5	3	4	1	0	2	1
4	4	3	3	2	1	0	0
5	5	4	4	3	0	1	0
6	4	3	3	3	4	0	1
7	4	2	2	2	0	1	1
8	4	3	3	1	1	2	1
9	4	3	3	2	0	3	1
10	5	2	2	0	0	1	3
11	5	4	3	3	1	1	1
12	5	3	2	2	0	1	2
13	5	4	3	2	0	3	1
14	4	3	3	2	1	2	0
15	5	2	2	3	1	1	0
16	5	3	2	0	1	0	0
17	5	3	1	3	0	1	1
18	5	2	2	2	1	1	0
19	5	3	3	1	1	0	1
20	4	2	3	0	2	1	0
21	4	3	2	2	1	1	1
22	5	5	3	1	1	0	1
23	4	2	1	2	2	0	1
24	5	3	4	3	1	1	1
25	5	3	3	1	3	0	1
26	5	4	4	2	2	0	2
27	5	4	3	0	0	2	1
28	5	4	4	3	1	1	1
29	5	3	2	2	0	1	1
30	5	4	4	3	0	0	3
Mean	4.7	3.06	2.66	1.86	0.9	0.93	0.96

Table 16 No. of comedons in each patient in group B of trial IV

THE EFFECT OF DRUGS ON PAPULES IN MODERATE CASES OF ACNE

In the group treated with oral **Doxycycline** along topical **Benzoyl peroxide** the arithmetical mean of papules in 30 patients was 3.43 before therapy and 1.7 at the end of sixth visit.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	2	2	1	1	2	3	2
2	3	2	2	2	3	2	1
3	4	3	1	1	2	0	3
4	3	1	1	2	1	0	2
5	4	3	2	3	1	2	0
6	4	2	3	3	2	2	3
7	3	3	2	1	2	0	0
8	4	2	3	2	3	1	3
9	4	1	3	1	0	2	2
10	3	1	3	2	3	2	3
11	4	2	3	3	1	3	1
12	4	3	3	0	1	2	2
13	2	4	2	1	3	1	2
14	3	3	1	2	2	1	0
15	4	2	1	3	1	2	1
16	3	1	1	2	3	1	2
17	4	3	2	3	2	0	2
18	4	2	0	1	2	2	3
19	3	1	4	3	3	1	2
20	4	2	2	3	2	1	2
21	4	3	1	3	2	3	3
22	3	3	2	2	2	1	2
23	4	2	1	1	1	3	3
24	2	3	2	1	2	2	2
25	3	4	1	0	1	3	1
26	4	3	1	1	1	0	2
27	3	2	2	2	2	1	1
28	4	1	2	3	0	3	0
29	3	2	2	1	1	2	0
30	4	3	3	2	1	1	1
Mean	3.43	2.3	1.9	1.83	1.73	1.56	1.7

Table 17 No. of papules in each patient in group A of trial IV

The value for the other group treated with oral Clindamycin along with topical Benzoyl peroxide are 3.6 and 0.90 at the end of sixth week respectively

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	2	1	1	0	0	0
2	2	3	3	1	1	0	1
3	3	1	1	1	1	2	2
4	4	3	1	0	2	1	1
5	3	2	3	2	0	0	1
6	4	1	2	1	1	1	2
7	4	3	1	2	2	1	1
8	3	2	2	3	1	1	1
9	4	3	1	0	0	0	0
10	4	2	2	2	1	0	1
11	3	3	2	2	1	2	0
12	4	1	0	0	1	1	0
13	4	2	2	2	0	2	1
14	3	3	1	1	1	1	0
15	4	4	2	1	1	0	1
16	3	3	0	0	1	1	1
17	4	2	2	1	2	0	1
18	4	1	0	1	0	1	2
19	4	2	2	0	1	2	2
20	4	1	0	1	0	1	1
21	4	3	0	2	0	2	1
22	4	1	3	0	1	0	0
23	4	3	1	0	1	1	1
24	4	1	3	1	1	1	1
25	4	1	2	1	1	1	0
26	2	2	0	0	1	2	1
27	3	1	2	1	2	1	2
28	4	3	1	2	0	1	2
29	3	1	2	2	1	0	0
30	4	3	1	0	1	1	0
Mean	3.6	2.1	1.43	1.03	0.86	0.9	0.9

Table 18 No. of papules in each patient in group B of trial IV

THE EFFECT OF DRUGS ON PUSTULES IN MODERATE CASES OF ACNE

The arithmetical mean of the number of pustules in the group treated with oral Doxycycline along with topical Benzoyl peroxide is seen as 3.3 before therapy and 1.06 at the end of sixth week.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	1	2	1	1	0	0
2	4	2	3	0	3	1	2
3	3	2	0	1	1	1	0
4	4	4	2	2	0	1	0
5	3	1	3	0	2	1	2
6	4	3	0	1	1	3	1
7	3	2	3	2	0	2	0
8	4	0	3	1	2	0	3
9	2	3	2	0	2	2	1
10	4	2	3	3	1	1	1
11	3	0	1	0	2	0	1
12	4	3	2	1	2	2	2
13	2	3	0	0	1	1	1
14	3	0	3	2	1	0	1
15	4	1	0	1	0	3	1
16	3	3	1	1	0	1	1
17	3	0	0	2	1	1	0
18	2	2	1	0	1	2	0
19	4	3	2	3	1	0	1
20	4	3	3	1	0	2	1
21	3	2	2	1	0	2	1
22	3	1	2	3	1	0	2
23	4	0	3	1	3	2	0
24	4	3	2	1	1	0	0
25	3	1	0	2	0	1	3
26	4	4	1	1	2	1	2
27	3	2	2	1	0	1	3
28	4	2	0	2	0	0	0
29	2	1	1	1	0	2	1
30	2	2	1	2	0	0	1
Mean	3.3	1.86	1.6	1.23	0.96	1.1	1.06

Table 19 No. of pustules in each patient in group A of trial IV

In the group treated with oral Clindamycin along with topical Benzoyl peroxide the values are 3.43 before therapy and 0.43 at the end of sixth week.

S.No.	visit 0	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
1	4	3	0	0	0	0	0
2	3	2	1	0	0	1	0
3	4	0	1	2	0	1	0
4	3	3	2	1	1	1	1
5	2	1	1	0	1	0	2
6	2	2	0	0	1	0	0
7	4	0	0	0	0	0	0
8	4	3	2	1	0	0	0
9	4	3	2	1	1	1	0
10	4	1	0	0	0	1	1
11	4	1	2	1	1	0	2
12	4	2	3	1	0	0	0
13	3	2	0	2	0	0	0
14	4	1	2	1	1	0	1
15	4	0	0	0	1	1	0
16	4	2	1	1	0	1	0
17	2	2	1	1	0	1	0
18	4	3	2	0	2	1	1
19	3	0	0	2	0	0	1
20	4	2	0	1	2	1	0
21	2	1	2	0	0	0	0
22	4	1	1	1	0	0	0
23	3	2	1	1	0	1	0
24	4	2	1	0	0	0	0
25	2	3	1	1	1	0	1
26	4	2	0	1	0	1	0
27	4	0	0	0	1	1	1
28	3	1	1	1	0	0	0
29	3	0	0	0	0	1	2
30	4	1	1	0	1	0	0
Mean	3.43	1.53	0.93	0.66	0.46	0.46	0.43

Table 20 No. of pustules in each patient in group B of trial IV

STATISTICAL ANALYSIS

Statistical analysis is done by using independent student t- test and the 'P' values are determined.

TRIAL I

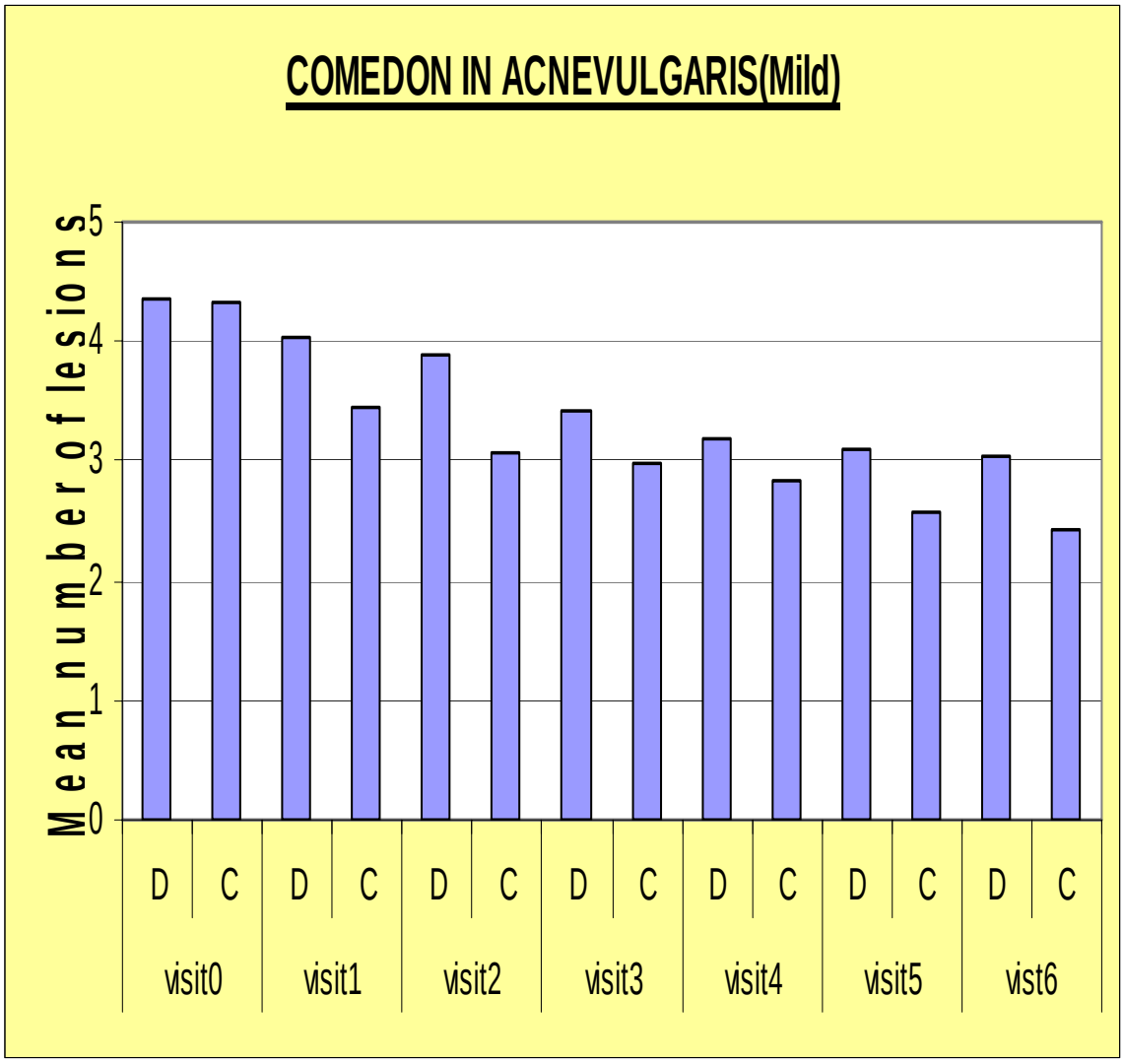
Comparision of number of comedons between group A & B of trial I

	group	N	Mean	Std. Deviation	Student Independent t-test
visit 0	D	30	4.40	.699	T=0.23
	C	30	4.33	.702	P=0.82 NOT SIGNIFICANT
visit 1	D	30	4.00	.810	T=2.11
	C	30	3.43	1.338	P=0.04 SIGNIFICANT
visit 2	D	30	3.80	.740	T=3.38
	C	30	3.06	1.153	P=0.001 SIGNIFICANT
visit 3	D	30	3.40	.708	T=2.05
	C	30	2.93	1.048	P=0.04 SIGNIFICANT
visit 4	D	30	3.16	.635	T=1.86
	C	30	2.86	.860	P=0.05 SIGNIFICANT
visit 5	D	30	3.13	.723	T=2.83
	C	30	2.96	.720	P=0.001 SIGNIFICANT
visit 6	D	30	3.06	.637	T=3.73
	C	30	2.83	.672	P=0.001 SIGNIFICANT

Table 21. Comparision of no. of comedons between group A & B of trial I.

D- Doxycyclin, C- Clindamycin.

Table 21 shows comparison done in relation to number of comedons between group A and B, which received oral Doxycycline and oral Clindamycin respectively. The 'P' value at the end of sixth week is 0.001 which is significant.



D = DOXYCYCLINE, C = CLINDAMYCIN

Figure 1 shows Reduction in number of comedons in Trial I

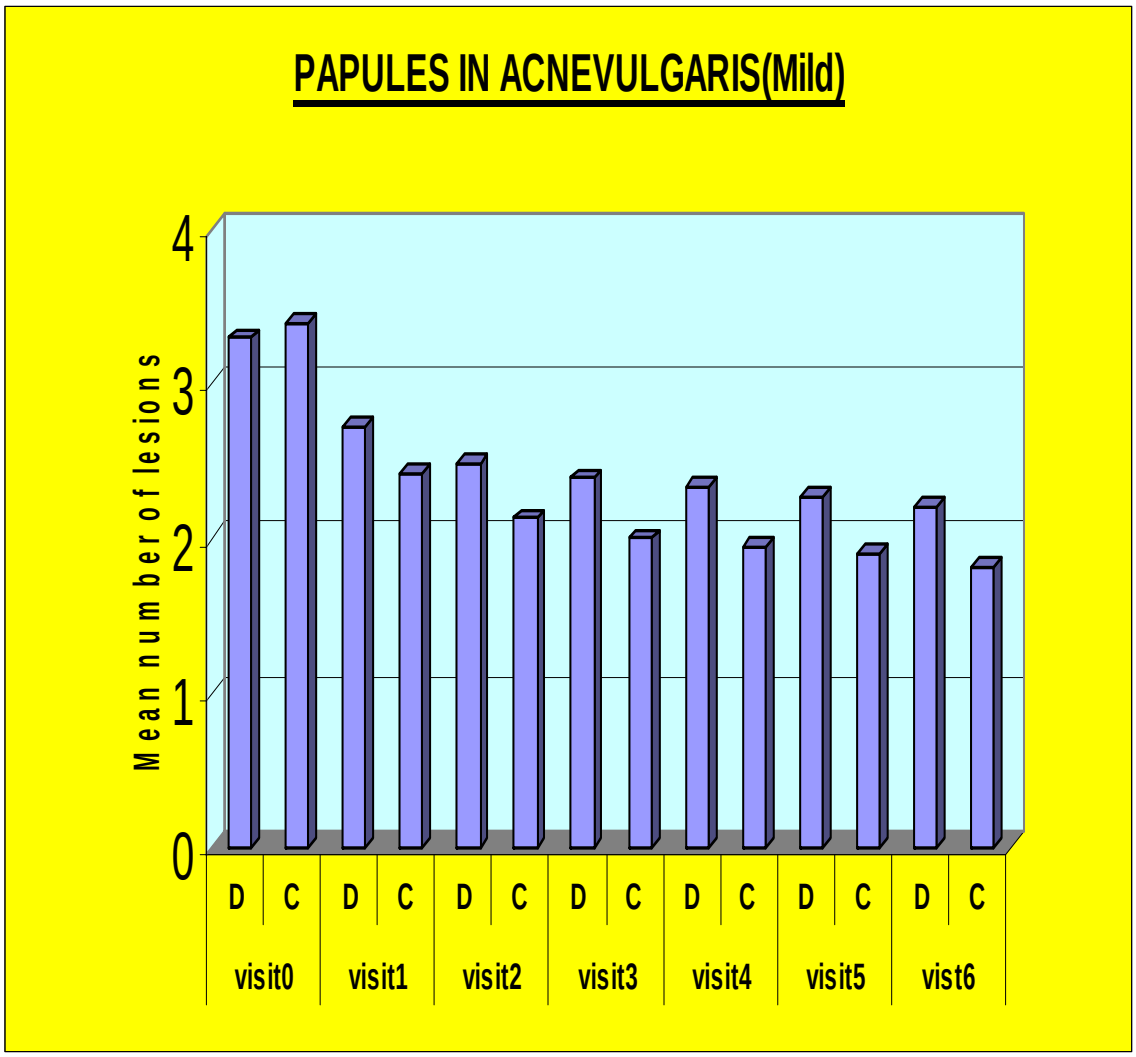
Comparision of number of papules between group A & B of trial I

	group	N	Mean	Std. Deviation	Student Independent t-test
visit 0	D	30	3.30	.728	T=0.48
	C	30	3.36	.667	P=0.63 NOT-SIGNIFICANT
visit 1	D	30	2.73	.674	T=1.76
	C	30	2.40	.720	P=0.48 NOT-SIGNIFICANT
visit 2	D	30	2.50	.834	T=1.87
	C	30	2.10	.670	P=0.07 NOT-SIGNIFICANT
visit 3	D	30	2.33	.747	T=1.99
	C	30	2.06	.790	P=0.05 SIGNIFICANT
visit 4	D	30	2.33	.795	T=2.01
	C	30	1.83	.846	P=0.04 SIGNIFICANT
visit 5	D	30	2.16	.740	T=2.01
	C	30	1.93	.870	P=0.04 SIGNIFICANT
visit 6	D	30	2.20	.683	T=2.02
	C	30	1.90	.806	P=0.05 SIGNIFICANT

Table 22. Comparision of no. of papules between group A & B of trial I.

D- Doxycyclin, C- Clindamycin.

The table No.22 shows comparison between Doxycycline and Clindamycin orally treated groups in Trial I, for papules, the 'P' value at the end of sixth week is 0.05 which is significant.



D =DOXYCYCLINE, C = CLINDAMYCINE.
Figure 2 shows Reduction in number of papules in Trial I

Trial II

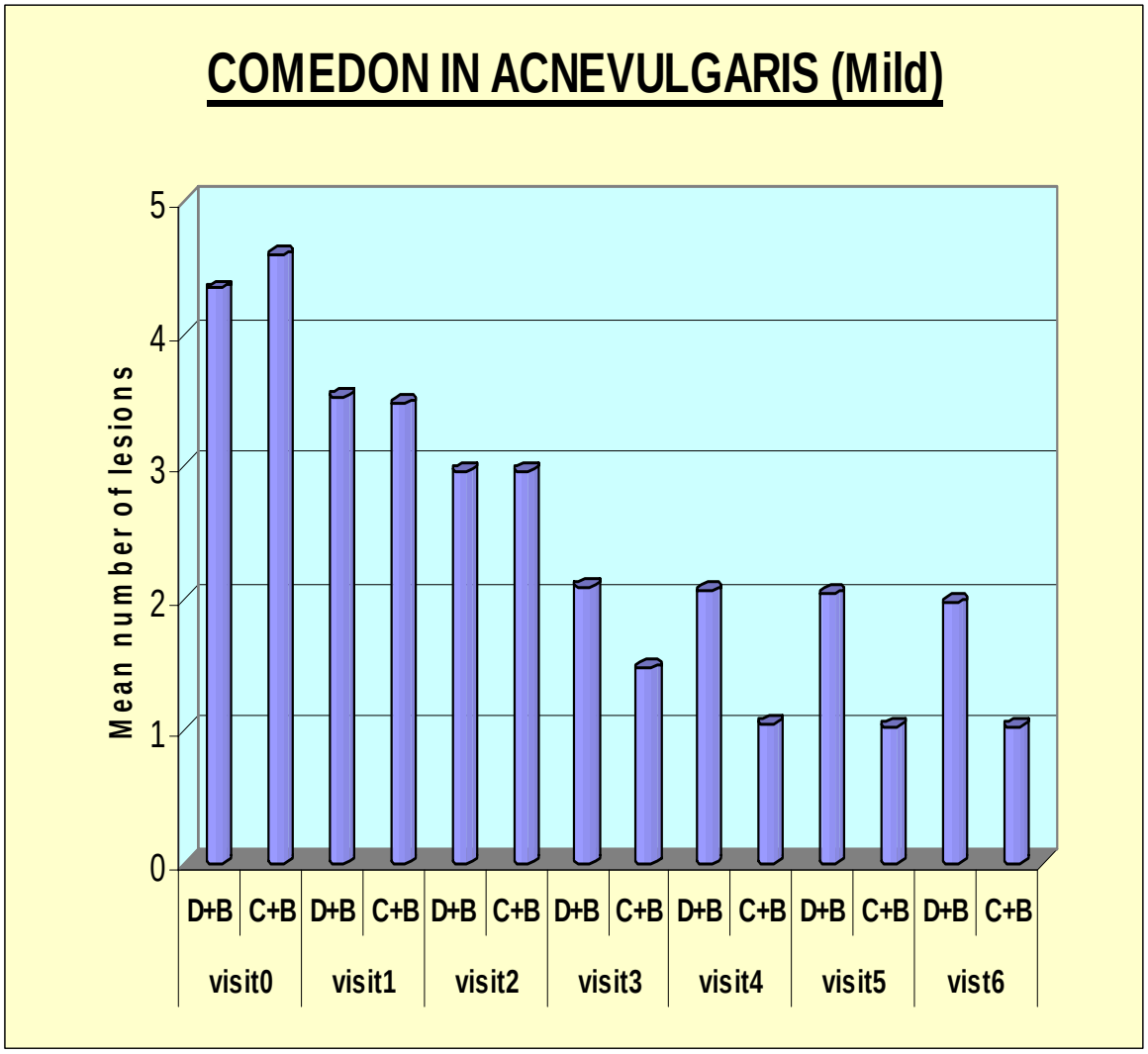
Comparision of number of comedons between group A & B of trial II

	group	N	Mean	Std. Deviation	Student Independent t-test
visit 0	D+B	30	4.33	.745	T=1.46
	C+B				P=0.15
		30	4.60	.615	NOT-SIGNIFICANT
visit 1	D+B	30	3.56	1.135	T=0.26
	C+B				P=0.79
		30	3.53	.761	NOT-SIGNIFICANT
visit 2	D+B	30	3.00	1.092	T=0.08
	C+B				P=1.00
		30	3.10	.933	NOT-SIGNIFICANT
visit 3	D+B	30	2.03	1.088	T=2.34
	C+B	30	1.46	1.047	P=0.02 SIGNIFICANT
visit 4	D+B	30	2.10	1.162	T=3.88
	C+B	30	1.06	.878	P=0.001 SIGNIFICANT
visit 5	D+B	30	2.10	1.121	T=4.07
	C+B	30	1.03	.822	P=0.001 SIGNIFICANT
visit 6	D+B	30	2.00	1.031	T=3.63
	C+B	30	1.10	1.031	P=0.001 SIGNIFICANT

Table 23. Comparision of no. of comedons between group A & B of trial II.

D- Doxycyclin, C- Clindamycin, B- Benzoyl peroxiode

In trial II, that is the group which has been treated oral Doxycyclin along with topical Benzoyl peroxide is compared with the other group treated withoral Clindamycin along with topical Benzoyl peroxide. The 'P' value at the end of sixth week in case of Comedon is 0.001, which is significant shown in table 23.



D =DOXYCYCLINE, C = CLINDAMYCIN, B = BENZOIL PEROXIDE

Figure 3 shows Reduction in number of comedons in Trial II

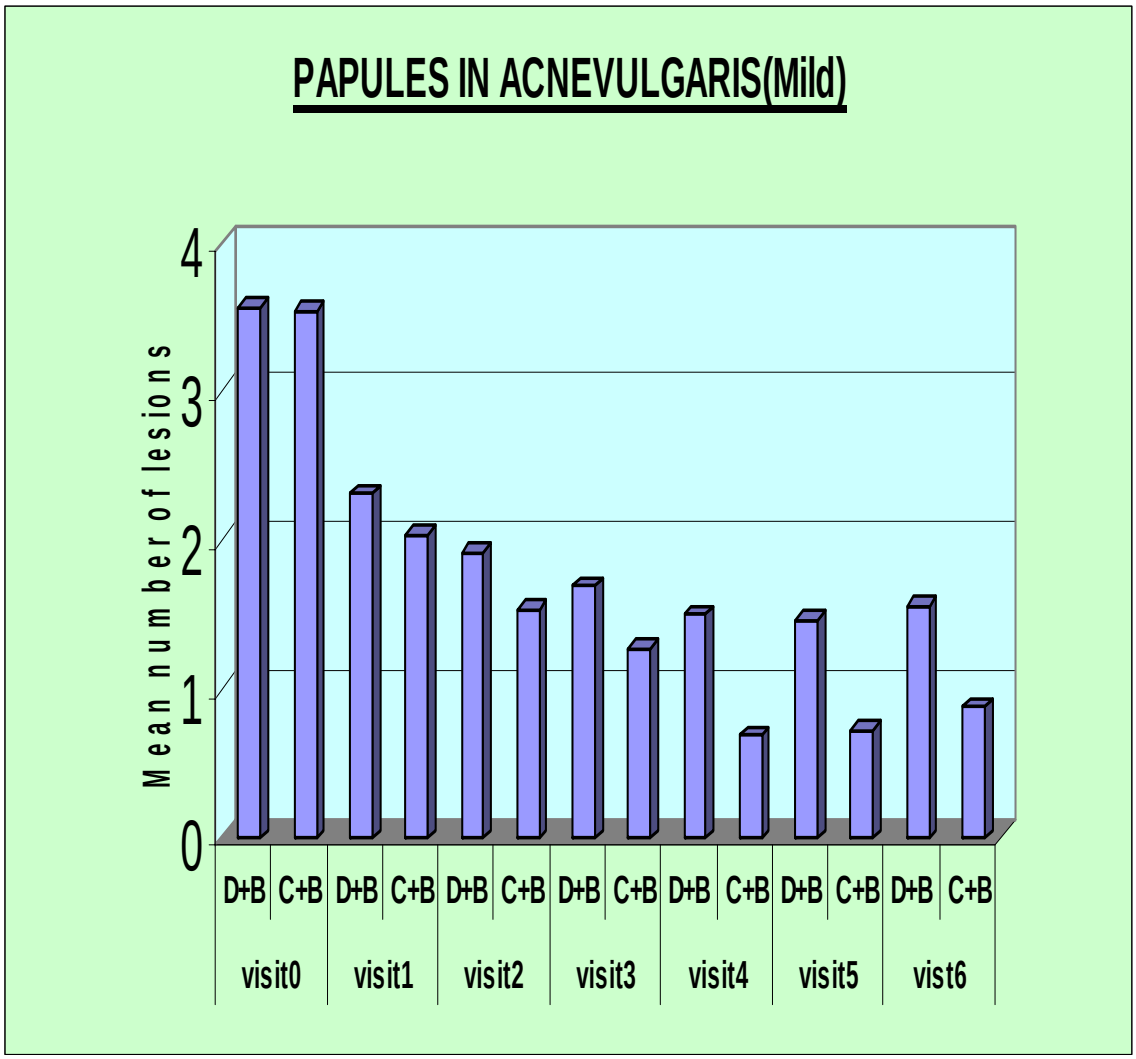
Comparision of number of papules between group A & B of trial II

	group	N	Mean	Std. Deviation	Student Independent t-test
visit 0	D+B	30	3.56	.504	T=0.25
	C+B				P=0.81
		30	3.56	.507	NOT-SIGNIFICANT
visit 1	D+B	30	2.30	.738	T=1.48
	C+B				P=0.14
		30	2.06	.782	NOT-SIGNIFICANT
visit 2	D+B	30	1.93	.734	T=1.73
	C+B				P=0.08
		30	1.60	.983	NOT-SIGNIFICANT
visit 3	D+B	30	1.73	.780	T=1.90
	C+B				P=0.06
		30	1.30	.924	NOT-SIGNIFICANT
visit 4	D+B	30	1.60	.950	T=3.66
	C+B	30	.70	.821	P=0.001 SIGNIFICANT
visit 5	D+B	30	1.50	.915	T=3.63
	C+B	30	.73	.729	P=0.001 SIGNIFICANT
visit 6	D+B	30	1.60	.840	T=3.54
	C+B	30	.86	.707	P=0.001 SIGNIFICANT

Table 24. Comparision of no. of papules between group A & B of trial II.

D- Doxycyclin, C- Clindamycin, B- Benzoyl peroxiode

In case of papules, the 'P' value determined at the end of sixth week is 0.001, which is also significant shown in table 24.



D = DOXYCYCLINE, C = CLINDAMYCINE, B = BENZOIL PEROXIDE.
Figure 4 shows Reduction in number of papules in Trial II

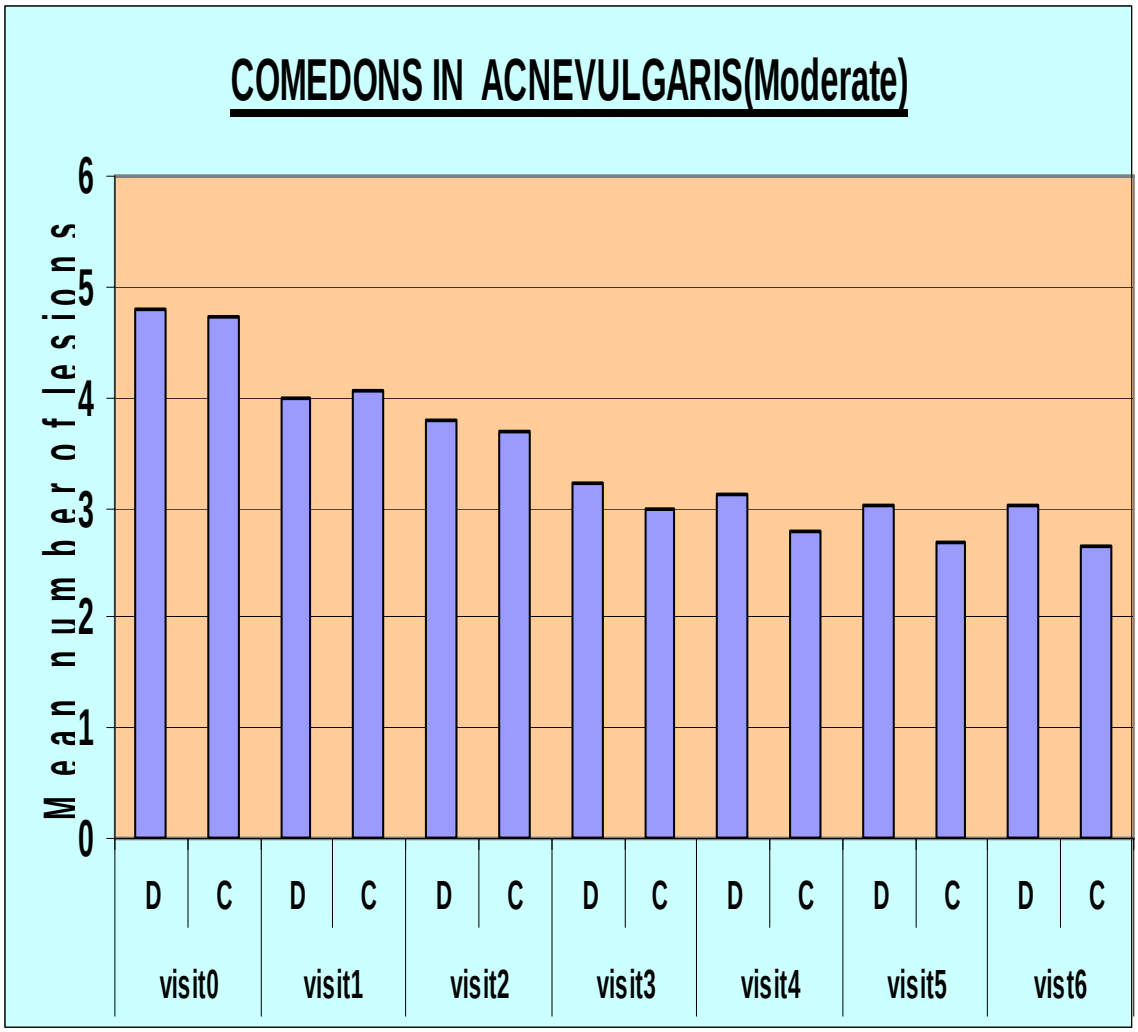
TRIAL III

Comparision of number of comedons between group A & B of trial III

	group	N	Mean	Std. Deviation	Student Independent t-test
visit 0	D	30	4.73	.407	T=0.81
	C	30	4.66	.461	P=0.42 NOT-SIGNIFICANT
visit 1	D	30	4.16	.871	T=0.27
	C	30	4.03	.964	P=0.79 NOT-SIGNIFICANT
visit 2	D	30	3.83	.714	T=0.6
	C	30	3.73	.871	P=0.59 NOT-SIGNIFICANT
visit 3	D	30	3.33	.774	T=1.96
	C	30	3.16	1.140	P=0.45 NOT-SIGNIFICANT
visit 4	D	30	3.13	.699	T=1.96
	C	30	2.96	.714	P=0.05 SIGNIFICANT
visit 5	D	30	3.10	.718	T=2.47
	C	30	2.73	0.72	P=0.01 SIGNIFICANT
visit 6	D	30	3.06	.626	T=1.96
	C	30	2.66	.73	P=0.05 SIGNIFICANT

Table 25. Comparision of no. of comedons between group A & B of trial III. D- Doxycyclin, C- Clindamycin.

In trial III, one group has received oral doxycyclin and other group has received oral Clindamycin in moderate cases of Comedons of acne vulgaris, the 'P' value in case of Comedon at the end of sixth week is 0.05, which is significant and is shown in table 25.



D = DOXYCYCLINE, C = CLINDAMYCIN.

Figure 5 shows Reduction in number of comedons in Trial III.

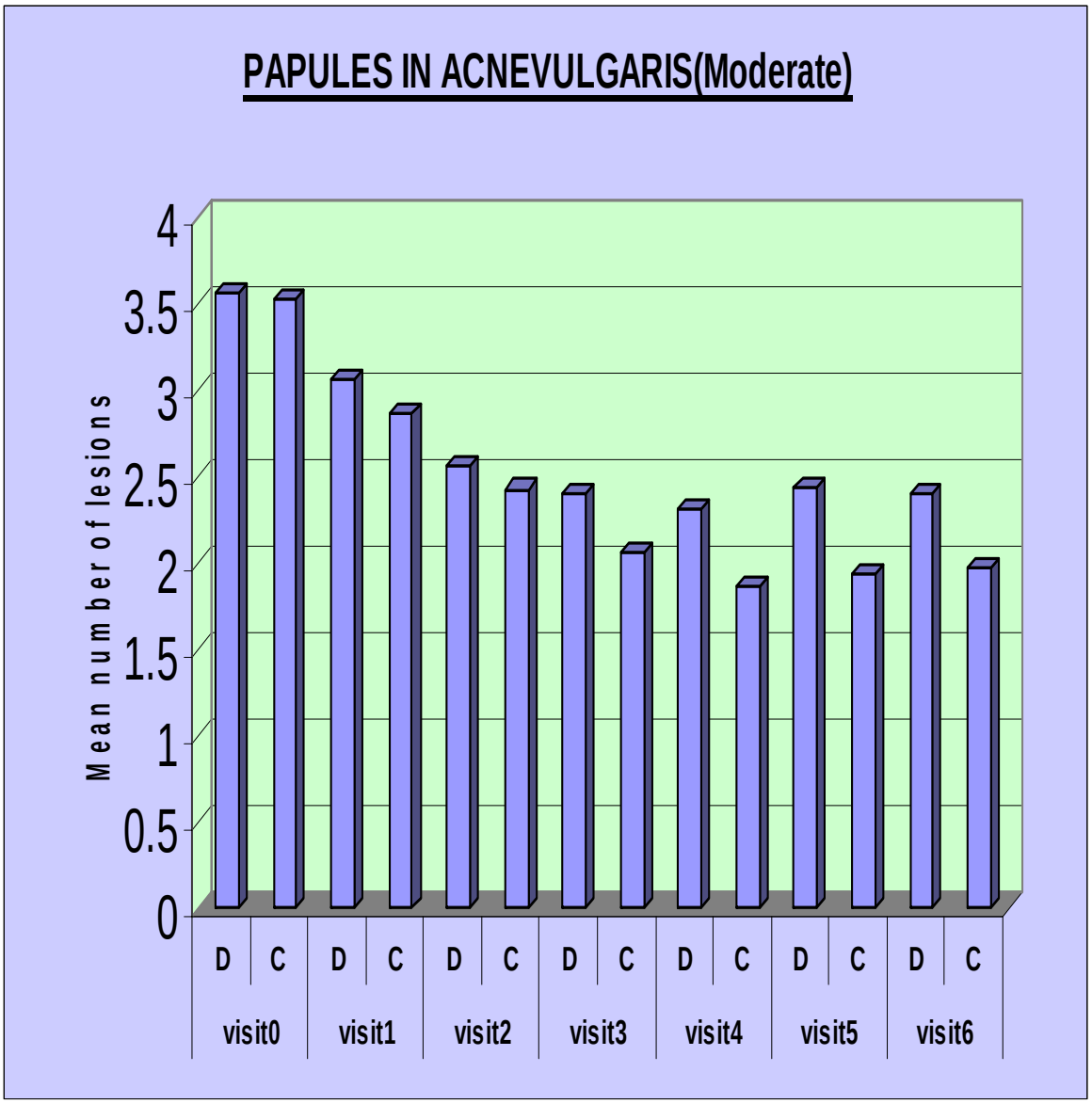
Comparision of number of papules between group A & B of trial III

	GROUP	N	Mean	Std. Deviation	Student Independent t-test
visit 0	D	30	3.60	.619	T=0.18
	C	30	3.53	.629	P=0.86 NOT-SIGNIFICANT
visit 1	D	30	3.03	.759	T=1.07
	C	30	2.86	.681	P=0.29 NOT-SIGNIFICANT
visit 2	D	30	2.63	.878	T=0.63
	C	30	2.43	.728	P=0.53 NOT-SIGNIFICANT
visit 3	D	30	2.36	.911	T=1.57
	C	30	2.06	.785	P=0.12 NOT-SIGNIFICANT
visit 4	D	30	2.33	.738	T=2.25
	C	30	1.86	.819	P=0.03 SIGNIFICANT
visit 5	D	30	2.43	.716	T=2.73
	C	30	1.93	.740	P=0.01 SIGNIFICANT
visit 6	D	30	2.36	.712	T=2.34
	C	30	1.96	.765	P=0.02 SIGNIFICANT

Table 26. Comparision of no. of papules between group A & B of trial III.

D- Doxycyclin, C- Clindamycin.

The ‘P’ value in case of papules at the end of sixth week is 0.02, which is significan and is shown in table 26.



D = DOXYCYCLINE, C = CLINDAMYCINE.

Figure 6 shows Reduction in number of papules in Trial III

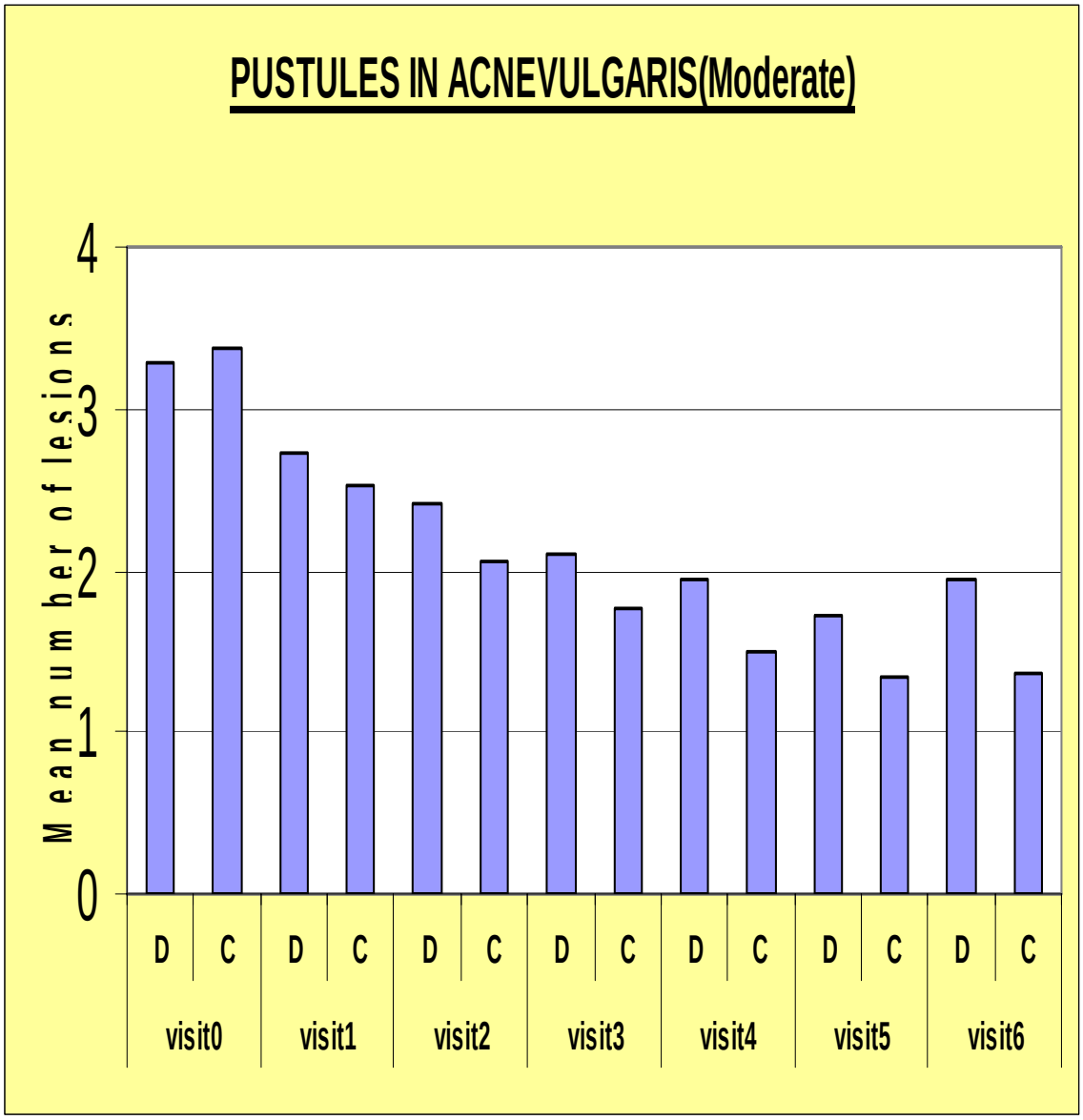
Comparision of number of pustules between group A & B of trial III

	group	N	Mean	Std. Deviation	Student Independent t-test
visit0	D	30	3.26	.77186	T=0.45
	C	30	3.36	.71840	P=0.65 NOT-SIGNIFICANT
visit1	D	30	2.66	.88843	T=0.94
	C	30	2.53	.62881	P=0.34 NOT-SIGNIFICANT
visit2	D	30	2.46	.66524	T=1.64
	C	30	2.06	.94443	P=0.10 NOT-SIGNIFICANT
visit3	D	30	2.06	.81752	T=1.57
	C	30	1.76	.81720	P=0.12 NOT-SIGNIFICANT
visit4	D	30	2.0	.87759	T=1.98
	C	30	1.50	.86103	P=0.05 SIGNIFICANT
visit5	D	30	1.76	.99139	T=1.99
	C	30	1.33	1.09334	P=0.05 SIGNIFICANT
visit6	D	30	2.03	1.16224	T=2.04
	C	30	1.36	1.03335	P=0.04 SIGNIFICANT

Table 27. Comparision of no. of pustules between group A & B of trial III.

D- Doxycyclin, C- Clindamycin.

In case of pustules, the 'P' value at the end of sixth week is 0.04, which is significant and is shown in table 27.



D = DOXYCYCLINE, C = CLINDAMYCIN.

Figure 7 shows Reduction in number of pustules in Trial III

TRIAL IV

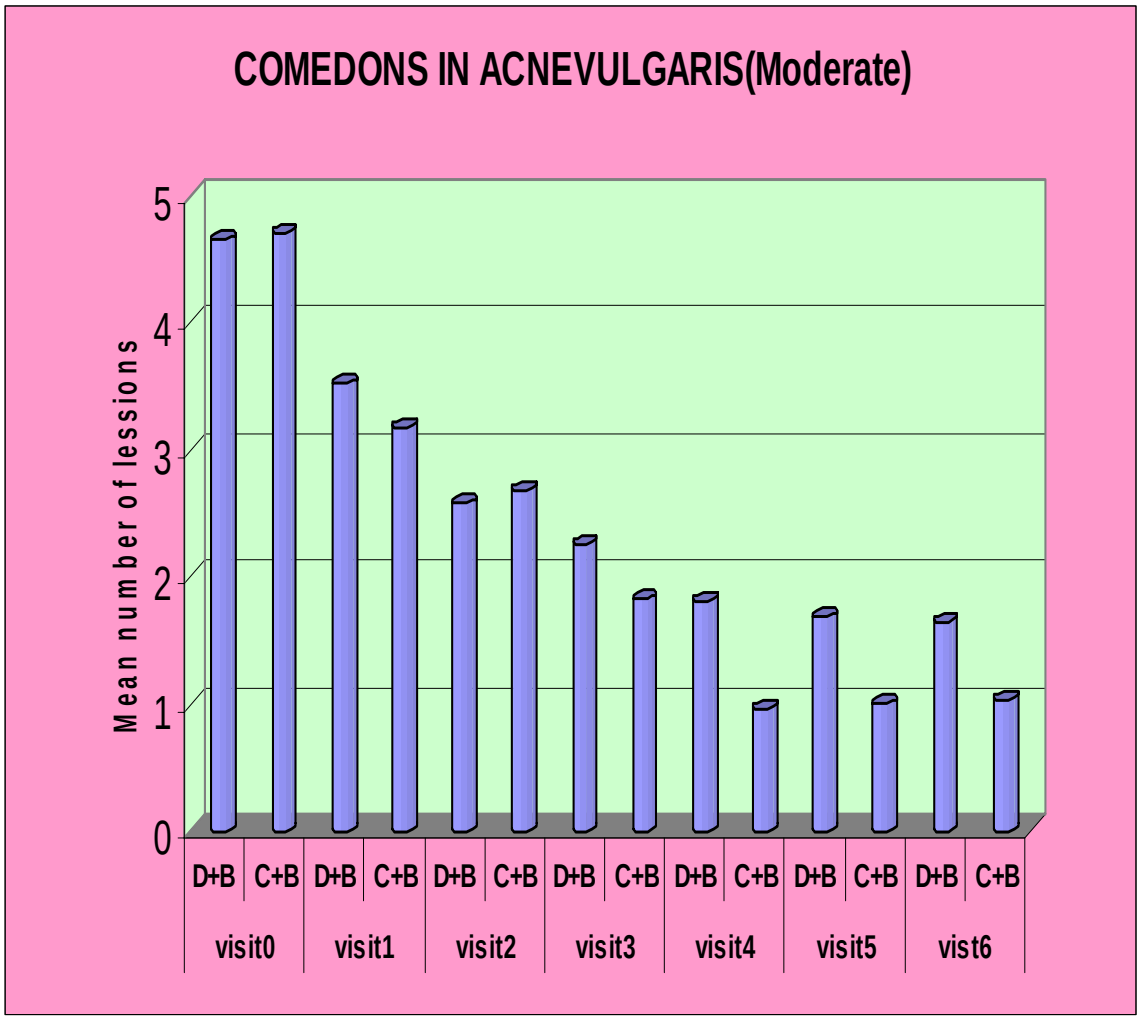
Comparision of number of comedons between group A & B of trial IV

	group	N	Mean	Std. Deviation	Student Independent t-test
visit 0	D+B	30	4.66	.486	T=0.56
	C+B	30	4.70	.460	P=0.57 NOT-SIGNIFICANT
visit 1	D+B	30	3.66	1.029	T=1.38
	C+B	30	3.06	.819	P=0.17 NOT-SIGNIFICANT
visit 2	D+B	30	2.63	1.285	T=0.33
	C+B	30	2.66	.905	P=0.74 NOT-SIGNIFICANT
visit 3	D+B	30	2.20	1.264	T=1.45
	C+B	30	1.86	1.020	P=0.15 NOT-SIGNIFICANT
visit 4	D+B	30	2.00	1.108	T=3.05
	C+B	30	.90	.999	P=0.003 SIGNIFICANT
visit 5	D+B	30	1.66	1.301	T=2.33
	C+B	30	0.93	.861	P=0.02 SIGNIFICANT
visit 6	D+B	30	1.86	1.279	T=2.11
	C+B	30	0.96	.881	P=0.04 SIGNIFICANT

Table 28. Comparision of no. of comedons between group A & B of trial IV.

D- Doxycyclin, C- Clindamycin, B- Benzoyl peroxide

One group which receives oral Doxycycline along with topical Benzoyl peroxide is compared to other group which has received oral Clindamycin and topical Benzoyl peroxide. This group includes only moderate cases. In case of Comedon, the 'P' value at the end of sixth week is 0.04, which is significant, shown in table 28.



D = DOXYCYCLINE, C = CLINDAMYCINE, B = BENZOIL PEROXIDE.

Figure 8 shows Reduction in number of comedons in Trial IV

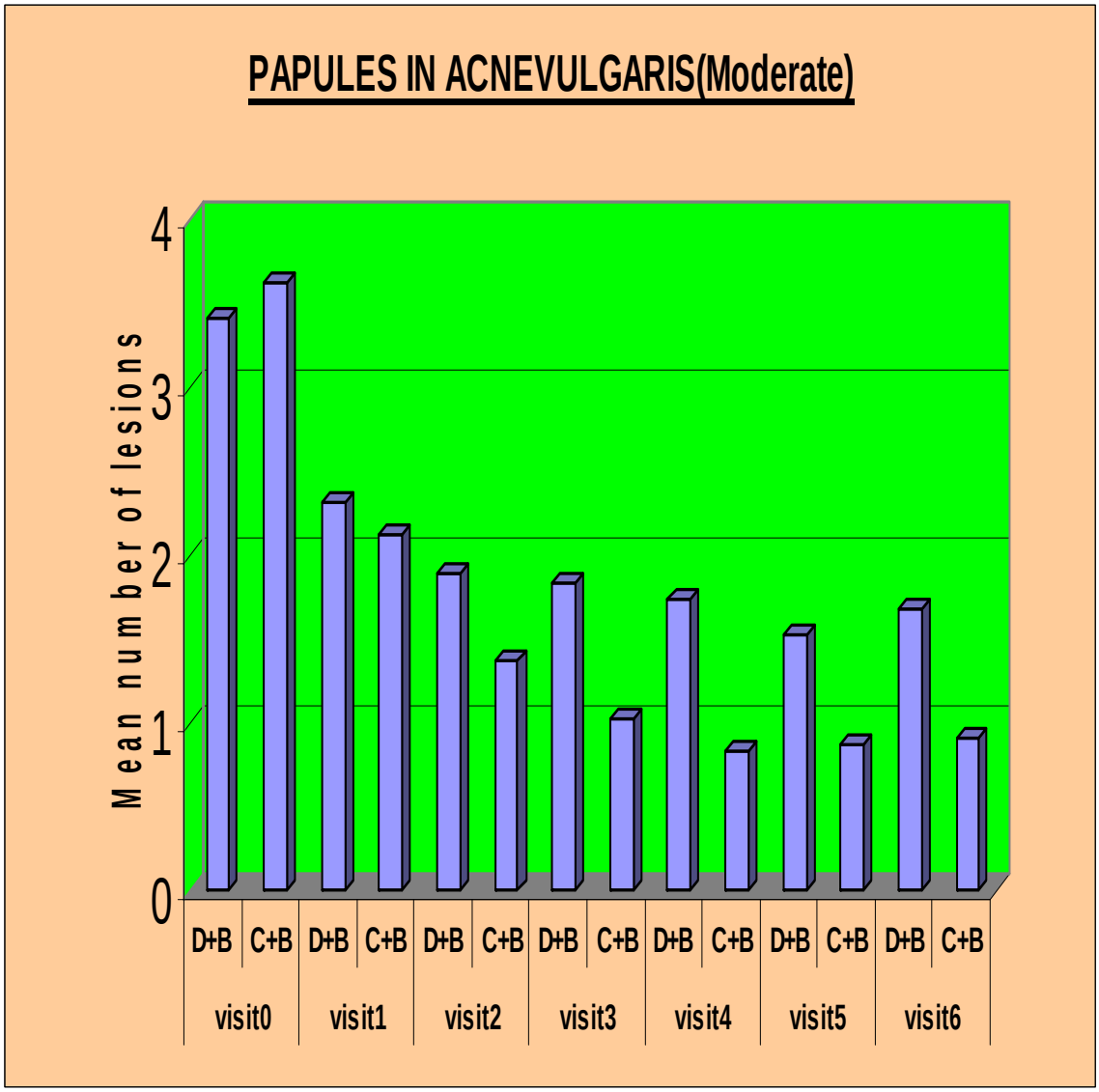
Comparision of number of papules between group A & B of trial IV

	GROUP	N	Mean	Std. Deviation	Student Independent t-test
visit 0	D+B	30	3.43	.672	T=1.27
	C+B	30	3.60	.609	P=0.21 NOT-SIGNIFICANT
visit 1	D+B	30	2.30	.871	T=0.88
	C+B	30	2.10	.907	P=0.38 NOT-SIGNIFICANT
visit 2	D+B	30	1.90	.908	T=2.22
	C+B	30	1.43	.976	P=0.04 SIGNIFICANT
visit 3	D+B	30	1.83	.934	T=3.34
	C+B	30	1.03	.822	P=0.001 SIGNIFICANT
visit 4	D+B	30	1.73	.855	T=4.76
	C+B	30	.86	.628	P=0.001 SIGNIFICANT
visit 5	D+B	30	1.56	1.029	T=2.89
	C+B	30	.90	.707	P=0.005 SIGNIFICANT
visit 6	D+B	30	1.70	1.013	T=3.54
	C+B	30	.90	.689	P=0.001 SIGNIFICANT

Table 29. Comparision of no. of papules between group A & B of trial IV.

D- Doxycyclin, C- Clindamycin, B- Benzoyl peroxide

In case of papules, the 'P' value at the end of sixth week is 0.001, which is significant, shown in table 29.



D = DOXYCYCLINE, C = CLINDAMYCINE, B =BENZOIL PEROXIDE.

Figure 9 shows Reduction in number of papules in Trial IV

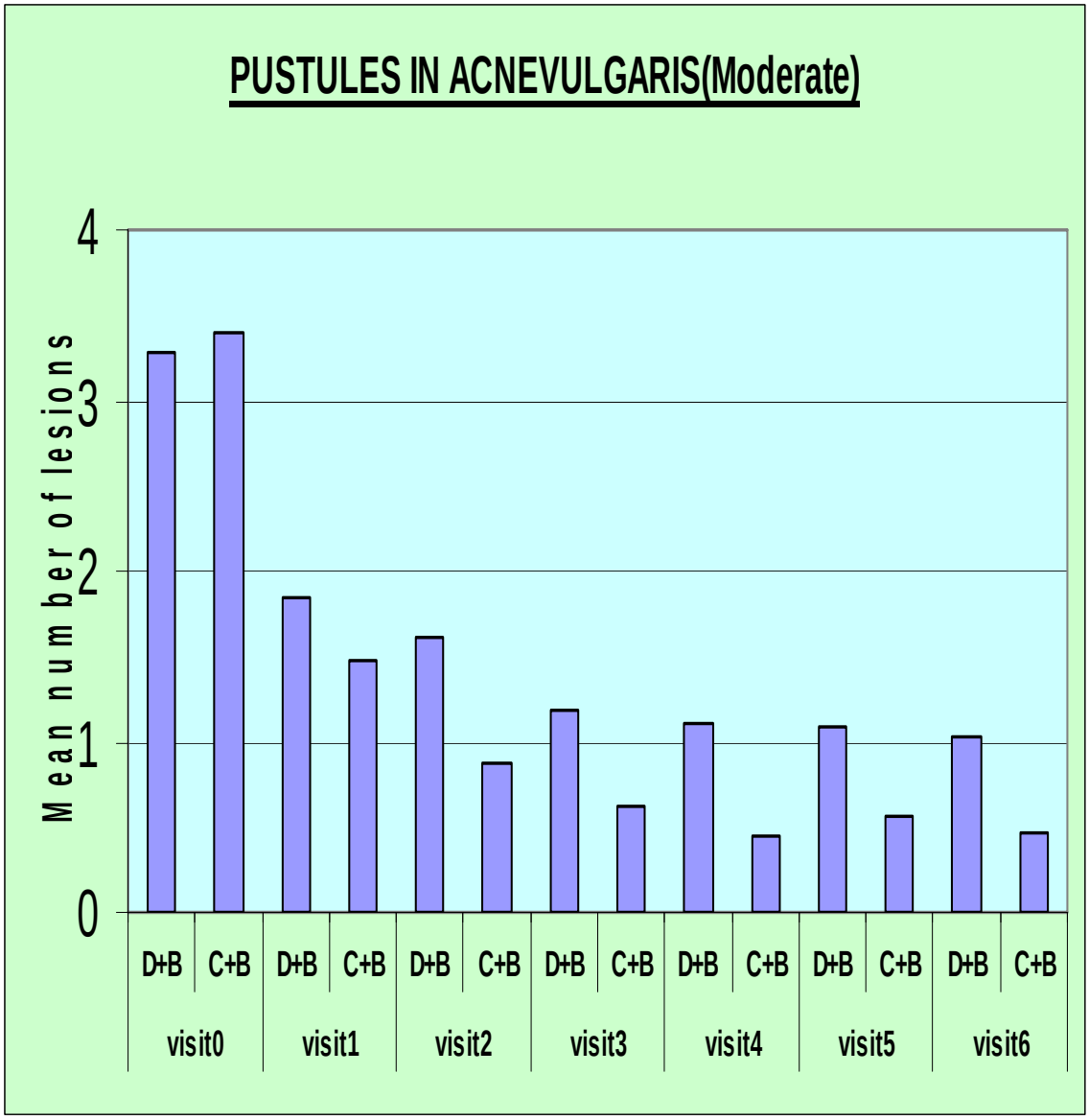
Comparision of number of pustules between group A & B of trial IV

	group	N	Mean	Std. Deviation	Student Independent t-test
visit0	D+B	30	3.30	.73908	T=0.60
	C+B	30	3.43	.79755	P=0.85 NOT SIGNIFICANT
visit1	D+B	30	1.86	1.18594	T=1.31
	C+B	30	1.53	1.04679	P=0.19 NOT-SIGNIFICANT
visit2	D+B	30	1.60	1.11587	T=2.93
	C+B	30	0.93	.87067	P=0.005 SIGNIFICANT
visit3	D+B	30	1.23	.90992	T=2.85
	C+B	30	0.66	.65991	P=0.006 SIGNIFICANT
visit4	D+B	30	0.96	.91228	T=2.71
	C+B	30	0.46	.61892	P=0.009 SIGNIFICANT
visit5	D+B	30	1.10	.90755	T=2.74
	C+B	30	0.46	.61892	P=0.008 SIGNIFICANT
visit6	D+B	30	1.06	.94812	T=2.67
	C+B	30	0.43	.71772	P=0.01 SIGNIFICANT

Table 30. Comparision of no. of pustules between group A & B of trial IV.

D- Doxycyclin, C- Clindamycin, B- Benzoyl peroxide

In case of pustules, the 'P' value at the end of sixth week is 0.001, which is significant, shown in table 30.



D = DOXYCYCLINE, C =CLINDAMYCINE, B = BENZOIL PEROXIDE.

Figure 10 shows reduction in number of pustules in Trial IV.

Results of Adverse effects

The patients were also followed up for the occurance of adverse effects. In fact one of the objective of the study is to find out, if Clindamycin is producing good results without causing unwanted effects when given in low doses of orally for a period of four weeks.

ADVERSE EFFECTS	0 VISIT	1ST VISIT	2ND VISIT	3RD VISIT	4TH VISIT	5TH VISIT	6TH VISIT	TOTAL NO. OF CASES
RASHES	0	0	0	0	0	0	0	0
URTICARIA	0	0	0	0	0	0	0	0
NAUSEA	0	1	1	2	1	2	2	9
VOMITING	0	1	2	1	1	1	1	7
ABDOMINAL PAIN	0	1	1	2	1	2	1	8
DIARRHOEA	0	0	1	1	1	1	2	6
DYSENTRY	0	0	1	1	1	1	1	5
DIZZINESS	0	0	0	0	0	0	0	0

Table 31. Adverse effects with clindamycin

Table 31 shows the occurance of adverse effects in the study group treated with Clindamycin.

The table shows the number of cases complaining of adverse effects mentioned during each visit for a period of six weeks.

The total number of patients reported with Nausea were 9, Vomiting were 7, Abdominal pain 8, Diarrhoea 6 and Dysentry 5.

7. DISCUSSION

The objective of the study is not only to find out the efficacy of a low dose of 50 mg Clindamycin given orally, but also to find out if this efficacy is obtained without producing the adverse effects for which the administration of Clindamycin is hesitated. The worst complication is pseudomembranous entero colitis.

Clindamycin produces very good effect in acne vulgaris and this is discussed later. These effects are produced without significant adverse effects.

In few cases reported as Nausea, Vomiting, Diarrhoea were clinically insignificant and they were self limiting. The patients revealed the occurrence of such effects only after questioning them specifically for such an effect.

If Diarrhoea, Abdominal pain had been severe they would have definitely reported to the investigator but no one reported. And all of them continued to take the drug without stopping. Here also it should be noted that if Nausea and Vomiting had been due to Pseudomembranous enterocolitis, the condition would have worsened with continuous intake.

But the symptoms were self limiting. Only three cases of Dysentry were prescribed tablet Metronidazole by their own doctor.

on analyzing the efficacy of oral Clindamycin, a low dose that is 50 mg administered daily for four weeks has definitely produced better results than Doxycycline administered as a single daily dose for 4 weeks.

There is significant reduction in the number of Comedons and papules in mild cases of acne vulgaris who have received only oral Clindamycin when compared to other group who have received only oral Doxycycline.

This is evident both in the clinical data which has been presented under the results column and also has been found to be statistically significant.

In moderate cases, also the significant improvement is seen in the group which is treated with oral Clindamycin. This is reflected as reduction in the number of Comedons, papules and pustules in the Clindamycin treated group, when compared to the other group which is Doxycycline treated control group. The role of Propionibacterium acne in pathogenesis of acne has already been discussed.

The anti microbials, Cap.Doxycycline and Cap.Clindamycin act in acne vulgaris by their effect on the Propionibacterium acne.

These antibiotics decrease the population of Propionibacterium acne which in turn leads to the inhibition of the bacterial lipases and this is followed by a decrease in concentration of free fatty acids .This produces less tissue inflammation and acne.

Since topically applied drugs are widely used in therapy of acne, in the trial groups in which the oral drug therapy was combined with topical Benzoyl peroxide and the outcome was analyzed.

Greater efficacy was obtained when oral Clindamycin was combined with topical Benzoyl peroxide. Doxycycline when used alone or in combination with Benzoyl peroxide has retained its efficacy, and the efficacy is greater when combined with topical Benzoyl peroxide.

Clindamycin either alone or in combination with topical Benzoyl peroxide 5% cream shows greater efficacy than Doxycycline either alone or in combination with topical Benzoyl peroxide 5% cream. The reason for lesser efficacy of Doxycycline could be due to development of resistance by Propionibacterium acne in some of the patients included in this trial.

The literature tells that there is increase in the resistance of Propionibacterium acne to antibiotics worldwide.

Clindamycin, though an anti microbial, shows greater efficacy in this study. This could be because Clindamycin oral therapy has not been used so far for acne vulgaris and probably the bacteria have not developed resistance.

The better results obtained in a group which has been treated with topical Benzoyl peroxide group could be definitely due to its anti bacterial action and direct anti inflammatory action.

8. CONCLUSION

The study has proved that a low dose of 50 mg of oral Clindamycin administered once a day for four weeks produces good results in acne vulgaris. The good results are obtained without unwanted adverse reactions. For many infections 150 to 300 mg are given 3 – 4 times a day produces many adverse effects.

In this trial the low dose of 50 mg used is not only highly effective, but also has not produced any significant adverse reactions. So far, the Clindamycin has only been used topically for acne vulgaris. This study encourages the use of low dose oral Clindamycin in acne vulgaris.

Future trials using Clindamycin in combination with the other topical agents like Tretinoin and Adapalene which have different mechanism of actions can be tried. Tretinoin reverses abnormal keratinizing changes in acne vulgaris. Adapalene has got comedolytic property.

This trial has been conducted as single centre trial and similar trials will promote wider use of oral Clindamycin in acne vulgaris.

This study proves the safety and efficacy of low dose of oral Clindamycin in acne vulgaris, and such low doses can also be tried for other infections where the causative organism responds to Clindamycin.

The following photos show Grade I & II case of Acne vulgaris in trail I & III

Before administration of oral Doxycycline

After four weeks administration of oral Doxycycline

The following photos show Grade I & II case of Acne vulgaris in trail II and IV

Before administration of oral Doxycycline with 5% Benzoil peroxide

After four weeks administration of oral Doxycycline with 5% Benzoil peroxide

The following photos show Grade I & II case of Acne vulgaris in trail I & III

Before administration of oral Clindamycin

After four weeks administration of oral Clindamycin

The following photos show Grade I & II case of Acne vulgaris in trial II & IV

Before administration of oral Clindamycin with 5% Benzoil peroxide

After four weeks administration of oral Clindamycin with 5% Benzoil peroxide

BIBLOGRAPHY

1. Tripathi. K.D. Drugs acting on skin and mucous membrane. Essentials of medical pharmacology, 5th ed.New Delhi:Jaypee brothers medical Publishers(p)Ltd;2003.p794-803.

2. E.Laurie Tolman, Acne and acneiform dermatoses, Mochella and Hurley Dermatology, 3rd ed, vol II,1 W.B.Saunders company publishers ;1992; 58: p 1477- 86.

3.Jowett S, Ryan T. skin disease and handicap :an analysis of the impact of skin condisons. Soc Sci Med 1985; 20 :p 425 - 29.

4. B Cunliffe WJ, Gould DJ. Prevalence of facial Acne vulgaris in late adolescence and in adults.BMJ 1979; 1: 1109 -10.

5. Ronald marks, Acne, rosacea and similer disorders, Roxburgh's common skin diseases, 17th ed, Arnold publishers. com; 2003;10: 149 - 61.

6. Gribbon EM, Cunliffee wJ, Holland K .Interaction of Propionibacterium acnes with skin lipids invitro.J Gen microbial 1993;139: 1745 - 50.

7 Geo. F. Brooks, Janet S. Butel, Stephen A . Morse,Jawetz,Melnick, & Adelberg's Medical microbiology, 23 rd ed, Mc Graw Hill - Medical publishing division; 2004:p 212 – 22.

8. Julie C Harper , First line therapy in inflammatory Acne, Contemporary issues in Acne management, vol I, Deriva C - Grace well publishers :July 2004 .

9.Buxton, Drake, Leyden and sheltie, Pochi , Shalita et al, E.Laurie Tolman , Acne and Acneiform dermatoses, Samuel L. Mochella ,Harry J. Hurley , Dermatology, 3 rd ed, W.B.Saunders company publishers; 58: p 1477- 86.

10.Imperato-McGinley j, Gautier T, Cal LQ et al.The androgen control of sebum production: Studies of subjects with dihydrotestosterone deficiency and complete androgen insensitivity. J Clin Endocrinol Metab 1993 ;76 :p 524.

11.Edward Abell, Inflammatory Diseases of the Epidermal Appendages and of Cartilage, David Elder, Rosalie Elenitsas, Christine Jaworsky, Bernett Johnson Jr, Lever's Histopathology of the skin,8th ed, Lippincott-Raven publishers;1997; p 403 – 419.

12.Leyden and shalita, E.Laurie Tolman ,Acne and Acneiform dermatoses, Samuel L. Mochella , Harry J. Hurley,Dermatology, 3 rd ed,58, W.B.Saunders company publishers:1992; p1477- 86.

13. Marples RR. The micro flora of the face and acne lesions. J Invest Dermatol 1974 ; 62:326 - 31.

14. Ronald marks, Acne, rosacea and similar disorders, Roxburgh's common skin diseases, 16th ed,Arnold publishers.com,2003; 10:149 - 61.

15. Strauss JS, Pochi PE, Downing DT. Acne perspectives. J Invest Dermatol 1974;62:321.

16. Holland KT,Greenman J,Cunliffe WJ.Growth of cutaneous propionibacteria on synthetic medium;growth yields and exoenzyme production.J Appl Bacteriol 1979; 47:383-94.

17.Geo. F. Brooks, Janet S. Butel, Stephen A . Morse, Jawetz, Melnick, & Adelberg's Medical Microbiology, 23 rd ed, Mc Graw Hill - Medical publishing division,2004;13: p 216,

18.Staphylococci, Connie R. Mohan, George manuselis , Text book of diagnostic microbiology, 2nd ed, W.B.Saunders company publishers;2000;10:p 330 - 42.

19.Microbial Diseases and Their control ,Lansing M.Prescott, John P.Harley, Donald A .Klein, Microbiology, 4th ed, Mc Graw Hill-Medical publishing division,37:p 780 – 798.

20. Shuster S.Acne:The ashes of a burnt out controversy.Acta Derm Venereol Suppl(Stockh) 1985;120 - 34.

21. Dirk B.Robertson, Howard I. Maibach, Dermatologic pharmacology .In: Bertram G.Katzung. Basic and clinical Pharmacology, 9th ed, New york: Lange Medical Books / Mc graw Hill, Medical publishing division; 2001: p1024

22. Tripathi K.D, Drugs acting on skin and mucous membrane, Essentials of Medical Pharmacology, 5th ed , New Delhi: Jaypee brothers medical publishers(p)Ltd;2003:p800.

23. Robert A.. Swerlick, Thomas J. Lawley, Acne vulgaris treatment , Eugene Braunwald, Anthony s. fauci, Dennis L.kasper, Stephen L.Hauser ,Dan L .Longo,J.Larry Jameson, Harrison's principles of Internal medicine, Vol I, 15 th ed, MC Graw Hill Medical publishing division, p 314 - 15.

24. Tripathi.K.D ,Drugs acting on skin and mucous membrane,Essentials of Medical pharmacology, 5th ed ,New Delhi:Jaypee brothers medical publishers(p)Ltd;2003.p800.

25. PRODIGY GUIDANCE-ACNE VULGARIS IN http: // www.clinical evidence.com /ce web/conditions /skd /1714 /1714-116.jsp. dt 08.05.2005.

26. Dirk B.Robertson, Howard I . Maibach, Dermatologic pharmacology .In: Bertram G.Katzung. Basic and clinical Pharmacology, 9th ed,New york:Lange Medical Books / Mc graw Hill, Medical publishing division; 2001;62:p1024

27. Tripathi.K.D, Drugs acting on skin and mucous membrane, Essentials of Medical Pharmacology, 5th ed ,New Delhi:Jaypee brothers medical publishers(p)Ltd;2003.p800.

28. Anti bacterial drugs, P.N.Bennett, M.J.Brown, Clinical Pharmacology,9th ed,Churchill Livingstone publication, 2003:12:p 215 – 35.

29. Henry F.Chambers,Antimicrobial agents: Protein synthesis Inhibitors and Miscellaneus antibacterial agents , Joeleg. hardman, Lee E. Limbird Good man &Gillman's , The Pharmacological Basis of Therapeutics, Alfred Goodman Gillman, 10th ed, MC Graw Hill – Medical publishing Division, 2001;47: p 1239 – 41.

30.Antibacterial Drugs, H.P.Rang, M.M.Dale, J.M Riter, P.K. Moore,Pharmacology, 5th ed, Churchil Livingstone publication,2003; 45 :p 635 – 53.

31.Joeleg.Hardman, Lee E. Limbird, Chemotherapy of microbial diseases, Good man & Gillman's The Pharmacological Basis of Therapeutics, Alfred Goodman Gillman, 10th ed, MC Graw Hill – Medical publishing Division,2001; 65: p 1239 – 71.

32.Tripathi.K.D, Drugs acting on skin and mucous membrane, Essentials of Medical pharmacology, 5th ed, New Delhi :Jaypee brothers medical publishers(p)Ltd;2003.p690.

33.Originalarticle: http://www.google.co.in/search?hl=en&q=acne+vulgaris+oral+clindamycin&btnG =Goole+search&meta=.page I of 2 dt 8/5/2005.

34. http://www.prodigy.nhs.uk/guidance.asp?gt= Acne% 20 vulgaris. Page 10& 11 of 50, dt 8/5/2005.

35. http://www.prodigy.nhs.uk/guidance.asp?gt=Acne% 20 vulgaris. Page 9 of 50, dt 8/5/2005.

APPENDIX I

Informed written consent form

I willing to participate in this study titled;the study of oral clindamycin in Acne vulgaris at my own will. I have understood the importance of this study.The objectives,importance and details of this study have been explained to me clearly by the investigator Dr.N.Arivazhagan, in my mother tongue. I am aware that if I wish to discontinue from the study at any point of time, I can do so. I also give permission to the researcher to use my medical records for any sort of publication.

Signature of the subject (or)
Date Of the parent/guardian .